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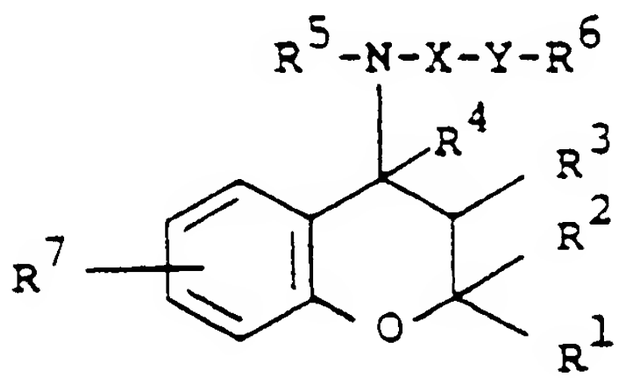
(54) Benzopyran derivatives and processes for preparation thereof.

(57) A compound of the formula :



wherein
R^1 and R^2 are each lower alkyl,
R^3 is hydroxy or acyloxy and R^4 is hydrogen, or
R^3 and R^4 are linked together to form a bond,
R^5 is hydrogen or lower alkyl and R^6 is hydrogen, lower alkyl or aryl, or
R^5 and R^6 are linked together to form lower alkylene,
R^7 is cyano, acyl, halogen, nitro or lower alkyl,
X is cyanoiminomethylene or sulfonyl, and
Y is single bond, thio, imino which may have lower alkyl,
with certain provisions, pharmaceutically acceptable salts thereof, processes for their preparation, and pharmaceutical compositions comprising them as an active ingredient.

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BENZOPYRAN DERIVATIVES AND PROCESSES FOR PREPARATION THEREOF

The present invention relates to novel benzopyran derivatives. More particularly, it relates to novel benzopyran derivatives which have pharmacological activities such as K^+ channel activator action and the like, to processes for preparation thereof, to a pharmaceutical composition comprising the same and to a use of the same as a medicament.

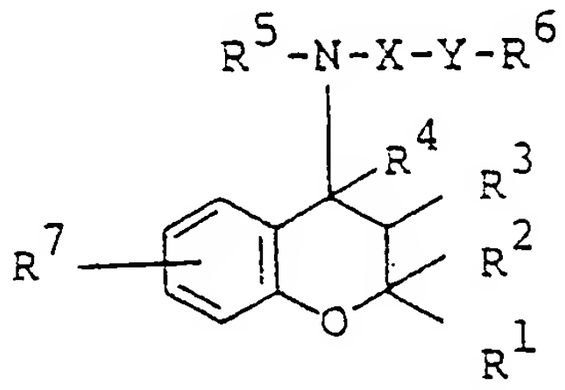
Accordingly, one object of the present invention is to provide novel benzopyran derivatives, which are useful as K^+ channel activator.

Another object of the present invention is to provide processes for preparation of said benzopyran derivatives.

A further object of the present invention is to provide a pharmaceutical composition comprising, as an active ingredient, said benzopyran derivatives.

Still further object of the present invention is to provide a use of said benzopyran derivatives as K^+ channel activator, especially vasodilating agent, useful for treating or preventing K^+ channel mediated diseases, for example, vascular disorders such as hypertension, angina pectoris, cardiac insufficiency, peripheral and cerebral vascular diseases, atherosclerosis, arrhythmia, and the like in human being or animals.

The benzopyran derivatives of the present invention are novel and can be represented by the formula (I) :

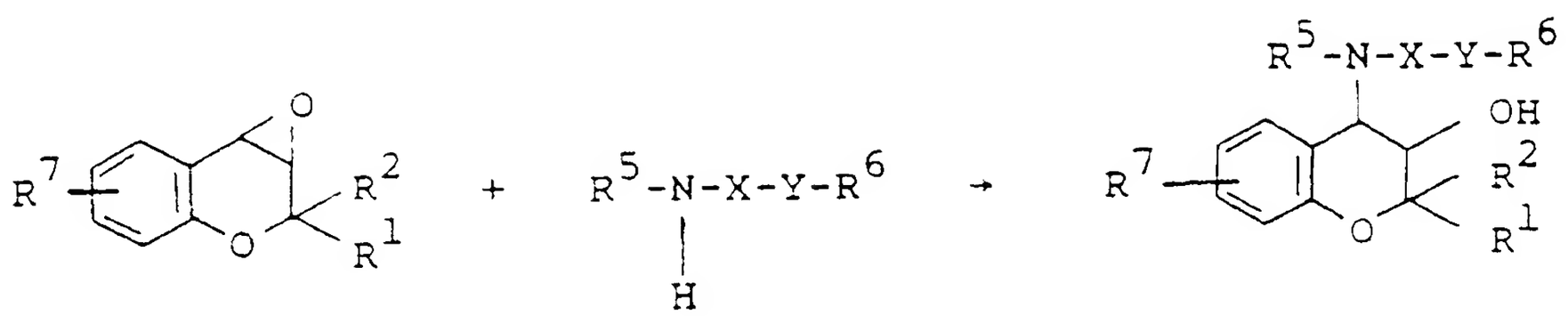


wherein
R^1 and R^2 are each lower alkyl,
R^3 is hydroxy or acyloxy and R^4 is hydrogen, or
R^3 and R^4 are linked together to form a bond,
R^5 is hydrogen or lower alkyl and R^6 is hydrogen, lower alkyl or aryl, or
R^5 and R^6 are linked together to form lower alkylene,
R^7 is cyano, acyl, halogen, nitro or lower alkyl,
X is cyanoiminomethylene or sulfonyl, and
Y is single bond, thio, imino which may have lower alkyl,
provided that i) when R^7 is cyano, X is cyanoiminomethylene and Y is thio or imino which may have lower alkyl, then R^5 is hydrogen or lower alkyl and R^6 is aryl; and ii) when R^7 is cyano, R^5 and R^6 are linked together to form lower alkylene and X is sulfonyl, then Y is thio or imino which may have lower alkyl.

With regard to the compound (I) of the present invention, it is to be noted that there may be one or more stereoisomeric pairs due to the presence of one or more asymmetric carbon atom(s) or double bond and these isomers or a mixture thereof are included within a scope of the compound (I) of the present invention.

According to the present invention, the object compound (I) can be prepared by the following processes :

Process 1 :

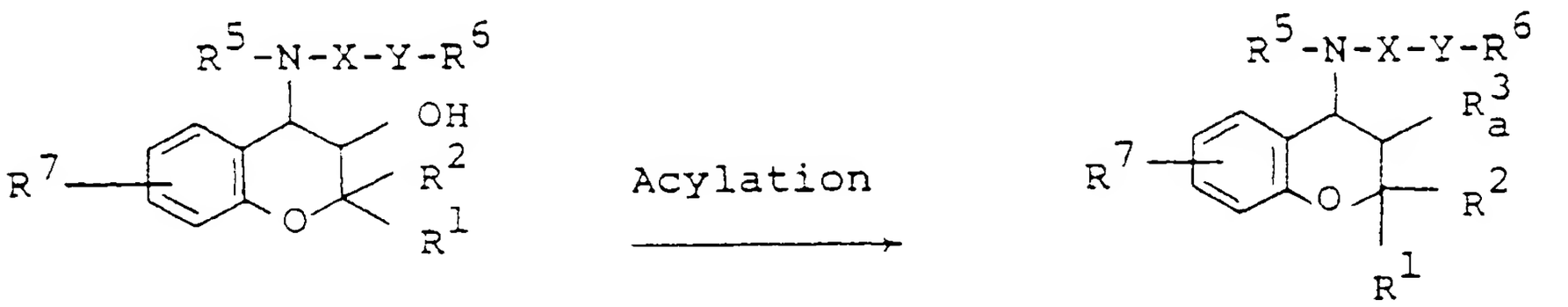


(II) + (III) → (I-a)

or a salt thereof

or a salt thereof

Process 2 :



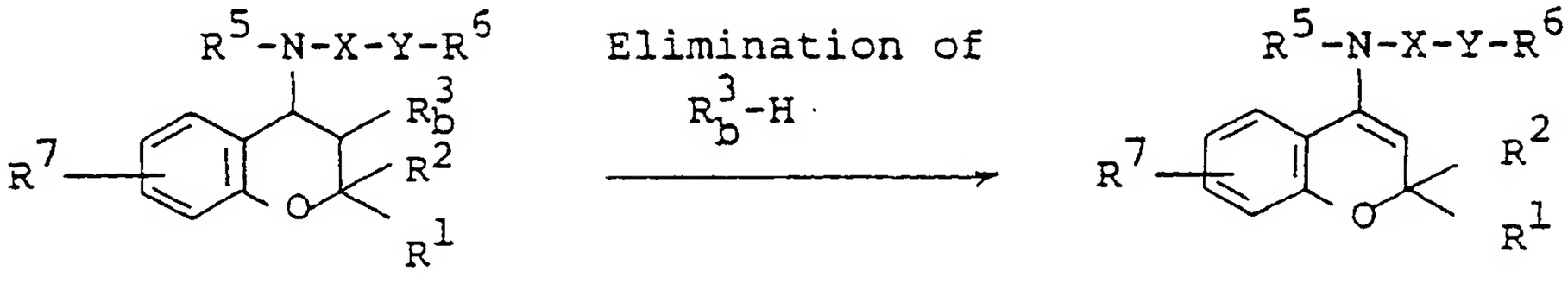
(I-a) → (I-b)

Acylation

or a salt thereof

or a salt thereof

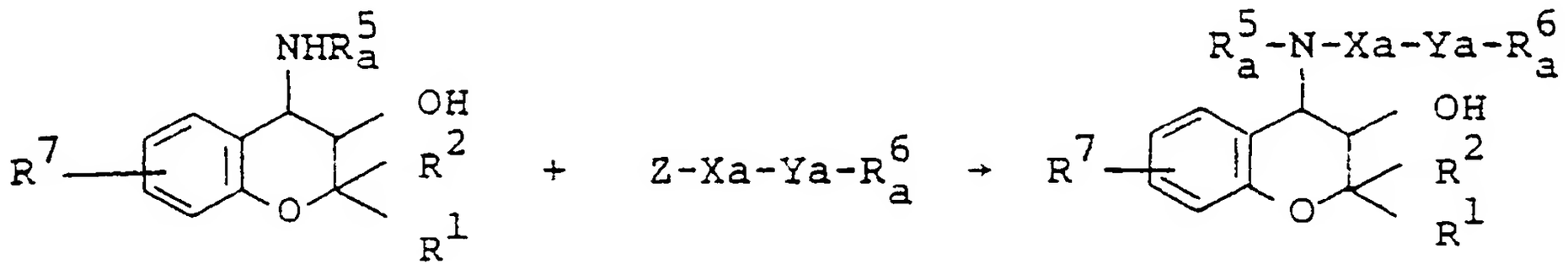
Process 3 :



(I-c)
or a salt thereof

(I-d)
or a salt thereof

Process 4 :

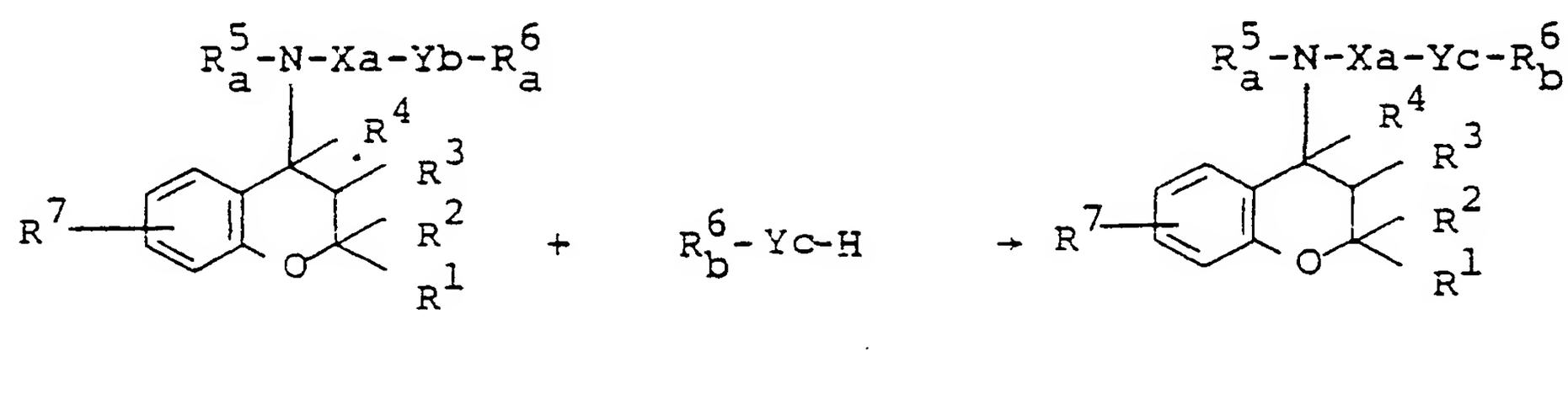


(IV)
or a salt thereof

(V)

(I-e)
or a salt thereof

Process 5 :

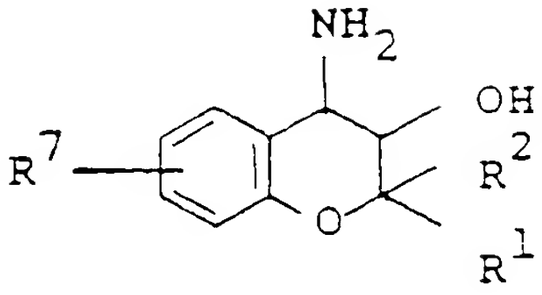


(I-f)
or a salt thereof

(VI)
or a salt thereof

(I-g)
or a salt thereof

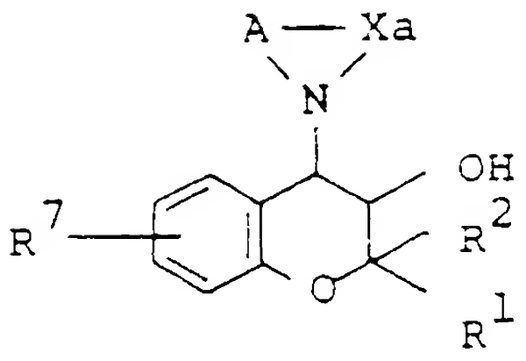
Process 6 :



(VII)

or a salt thereof

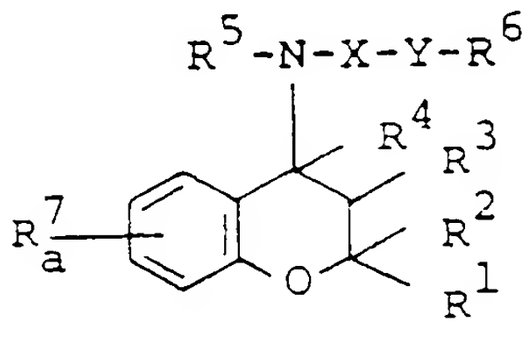
+ Z-Xa-A-R^8 (VIII)



(I-h)

or a salt thereof

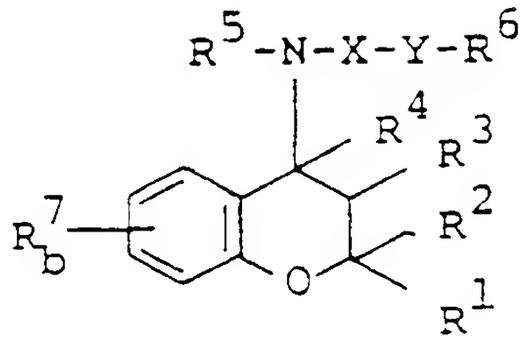
Process 7 :



(I-i)

or a salt thereof

Removal of lower alkyl



(I-j)

or a salt thereof

wherein
R^1, R^2, R^3, R^4, R^5, R^6, R^7, X and Y are each as defined above,
R^3_a is acyloxy,
R^3_b is hydroxy or acyloxy,
R^5_b is hydrogen or lower alkyl,
R^6_a and R^6_b are each hydrogen, lower alkyl or aryl,
R^7_a is lower alkoxycarbonyl,
R^7_b is carboxy,
R^8 acid residue,
Xa is cyanoiminomethylene,
Ya is single bond or thio,
Yb is thio,

Yc is imino which may have lower alkyl,
Z is leaving group, and
A is lower alkylene.

Suitable salts of the compound (I), (I-a), (I-b), (I-c), (I-d), (I-e), (I-f), (I-g), (I-h), (I-i), (I-j), (III), (IV), (VI) and (VII) are conventional non-toxic, pharmaceutically acceptable salts and may include a salt with a base or an acid addition salt such as a salt with an inorganic base, for example, an alkali metal salt (e.g. sodium salt, potassium salt, cesium salt, etc.), an alkaline earth metal salt (e.g. calcium salt, magnesium salt, etc.), an ammonium salt; a salt with an organic base, for example, an organic amine salt (e.g. triethylamine salt, pyridine salt, picoline salt, ethanolamine salt, triethanolamine salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt, etc.), etc.; an inorganic acid addition salt (e.g. hydrochloride, hydrobromide, sulfate, phosphate, etc.); an organic carboxylic or sulfonic acid addition salt (e.g. formate, acetate, trifluoroacetate, maleate, tartrate, methanesulfonate, benzenesulfonate, p-toluenesulfonate, etc.); a salt with a basic or acidic amino acid (e.g. arginine, aspartic acid, glutamic acid, etc.); and the like.

In the above and subsequent descriptions of the present specification, suitable examples and illustrations of the various definitions which the present invention include within the scope thereof are explained in detail as follows.

The term "lower" is intended to mean 1 to 6 carbon atoms, preferably 1 to 4 carbon atoms, unless otherwise indicated.

Suitable "lower alkyl" may include straight or branched one, having 1 to 6 carbon atom(s), such as methyl, ethyl, propyl, isopropyl, butyl, t-butyl, pentyl, hexyl, or the like, in which the preferred one is methyl, ethyl or propyl.

Suitable "lower alkylene" and the lower alkylene moiety formed by linkage of R^5 and R^5 may include methylene, ethylene, propylene, trimethylene, tetramethylene, pentamethylene, hexamethylene, or the like, in which the preferred one is methylene, ethylene or trimethylene.

Suitable "acyl" and acyl moiety of "acyloxy" may include aliphatic, aromatic, araliphatic, heterocyclic and heterocyclic-aliphatic acyl derived from carboxylic, carbonic, carbamic and sulfonic acid, and the preferable example of said acyl moiety may be carboxy, lower alkanoyl (e.g. formyl, acetyl, propionyl, butyryl, pentanoyl, hexanoyl, etc.), lower alkylsulfonyl, (e.g. mesyl, ethylsulfonyl, propylsulfonyl, butylsulfonyl, hexylsulfonyl, etc.), N,N-di(lower)alkylsulfamoyl (e.g. dimethylsulfanoyl, diethylsulfamoyl, dipropylsulfamoyl, diisopropylsulfamoyl, dihexylsulfamoyl, etc.), lower alkoxycarbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, etc.), and the like.

Suitable "halogen" means fluoro, chloro, bromo and iodo.

Suitable "leaving group" may include lower alkylthio (e.g. methylthio, ethylthio, etc.), and the like.

Suitable "aryl" may include phenyl, tolyl, xylyl, cumenyl, mesityl, naphthyl, and the like, preferably one having 6 to 10 carbon atoms, in which the preferred one is phenyl.

Suitable "acid residue" may include halogen as mentioned above, acyloxy (e.g. tosyloxy, mesyloxy, etc.) and the like.

Suitable "lower alkoxycarbony" may include methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, and the like.

The processes 1 to 7 for preparing the object compound (I) of the present invention are explained in detail in the following.

Process 1 :

the object compound (I-a) or a salt thereof can be prepared by reacting the compound (II) with the compound (III) or a salt thereof.

The present reaction is usually carried out in the presence of a base such as alkyl lithium (e.g. n-butyl lithium, etc.), alkali metal hydride (e.g. sodium hydride, potassium hydride, etc.), tri(lower)alkylamine (e.g. trimethylamine, triethylamine, etc.), pyridine or its derivative (e.g. picoline, lutidine, 4-dimethylaminopyridine etc.), or the like, in case that the compound (III) is used in a free form.

The present reaction is usually carried out in a solvent such as dioxane, dimethyl sulfoxide, dimethylformamide, diethylformamide, dimethylacetamide, benzene, tetrahydrofuran, or any other solvent which does not adversely affect the reaction. In case that the base to be used in liquid, it can also be used as a solvent.

The reaction temperature is not critical and the reaction is usually carried out under cooling, at ambient temperature or under heating.

The object compound (I-a) can be used as a starting compound of the Process 2 mentioned hereinbelow with or without isolation.

Process 2 :

The object compound (I-b) or a salt thereof can be prepared by acylating the compound (I-a) or a salt thereof.

The acylating agent used in this reaction is a conventional one which is capable of introducing the acyl group as mentioned above into a hydroxy, and may preferably be lower alkanecarboxylic acid, lower alkanesulfonic acid, their acid anhydride, their acid halide, their activated ester, their acid amide, and the like.

In case that the acylating agent is used in a free acid form, the reaction is usually carried out in the presence of a conventional condensing agent such as carbodiimide compounds, and the like.

This reaction is preferably carried out in the presence of a base such as those given in the explanation of the Process 1 mentioned above.

This reaction is usually carried out in a solvent such as dimethylformamide, tetrahydrofuran, pyridine or any other solvent which does not adversely affect the reaction.

The reaction temperature is not critical, and the reaction can be carried out under cooling to warming.

Process 3 :

The object compound (I-d) or a salt thereof can be prepared by subjecting the compound (I-c) or a salt thereof to elimination reaction of the compound R_5^3 -H.

The elimination reaction can usually be carried out by an inorganic base such as alkali metal hydride (e.g. sodium hydride, potassium hydride, etc.), or the like, and an organic base such as trialkylamine (e.g. trimethylamine, triethylamine, etc.), picoline, N-methylpyrrolidine, N-methylmorpholine, 1,5-diazabicyclo-[4.3.0]non-5-one, 1,4-diazabicyclo[2.2.2]octane, 1,5-diazabicyclo[5.4.0]undecene-5, 1,8-diazabicyclo[5.4.0]-undec-7-ene or the like.

This reaction can be carried out in a conventional solvent which does not adversely affect the reaction such as those given in the explanation of Process 1.

The reaction temperature is not critical and the reaction is usually carried out under cooling, at ambient temperature or under heating.

Process 4 :

The object compound (I-e) or a salt thereof can be prepared by reacting the compound (IV) or a salt thereof with the compound (V).

This reaction is usually carried out in a solvent such as alcohol (e.g. methanol, ethanol, etc.), N,N-dimethylformamide, tetrahydrofuran, toluene or any other solvent which does not adversely affect the reaction.

The reaction may be carried out in the presence of an inorganic or an organic base such as tri(lower)-alkylamine (e.g. trimethylamine, triethylamine, etc.), pyridine or its derivative (e.g. picoline, lutidine, 4-dimethylaminopyridine, etc.), or the like. In case that the base to be used is liquid, it can also be used as a solvent.

The reaction temperature is not critical, and the reaction can be carried out under warming or heating.

Process 5 :

The object compound (I-g) or a salt thereof can be prepared by reacting the compound (I-f) or a salt thereof with the compound (VI) or a salt thereof.

The reaction may be carried out in the presence of an inorganic or an organic base such as tri(lower)-alkylamine (e.g. trimethylamine, triethylamine, etc.), pyridine or its derivative (e.g. picoline, lutidine, 4-dimethylaminopyridine, etc.), or the like.

This reaction is usually carried out in a solvent such as alcohol (e.g. methanol, ethanol, etc.), dimethyl sulfoxide, N,N-dimethylformamide, tetrahydrofuran or any other solvent which does not adversely affect the reaction.

In case that the compound (VI) or a salt thereof or the base to be used is liquid, it can also be used as a solvent.

The reaction temperature is not critical, and the reaction can be carried out under warming or heating.

Process 6 :

The object compound (I-h) or a salt thereof can be prepared by reacting the compound (VII) or a salt thereof with the compound (VIII).

This reaction can be carried out in substantially the same manner as Process 4, and therefore the reaction mode and reaction conditions (e.g. solvents, bases, reaction temperature, etc.) of this reaction are to be referred to those as explained in Process 4.

Process 7 :

The object compound (I-j) or a salt thereof can be prepared by subjecting the compound (I-i) or a salt thereof to removal reaction of lower alkyl.

The reaction may be carried out in the presence of alkali metal halide (e.g. lithium iodide, etc.).

The reaction may be carried out in the presence of an inorganic or an organic base such as tri(lower)-alkylamine (e.g. trimethylamine, triethylamine, etc.), pyridine or its derivative (e.g. picoline, lutidine, 4-dimethylaminopyridine, etc.), or the like.

This reaction is usually carried out in a solvent such as alcohol (e.g. methanol, ethanol, etc.), dimethyl sulfoxide, N,N-dimethylformamide, tetrahydrofuran or any other solvent which does not adversely affect the reaction.

The reaction temperature is not critical, and the reaction can be carried out under warming or heating.

Among the starting compounds (II), (III), (IV) and (VII) some of them are new and such compounds can be prepared by the methods of Preparations mentioned below.

The object compound (I) of the present invention can be isolated and purified in a conventional manner, for example, extraction, precipitation, fractional crystallization, recrystallization, chromatography, and the like.

With regard to the compound (I) of the present invention, when R^3 is hydroxy or acyloxy and R^4 is hydrogen, it is preferred that the hydroxy or acyloxy at the third position of 1-benzopyran nucleus and a group of the formula : $R^5-\underset{|}{N}-X-Y-R^6$ at the fourth position of the same are mutually trans, and further it is most preferred they being the (3S,4R)-isomer.

The optical resolution of the isomers of the compound (I) can be carried out by a conventional method such as a resolution by reacting a mixture of isomers with an optically active reagent. Such reagents include optically active acids (e.g., benzyloxycarbonyl-L-phenylalanine, etc.) or acid derivatives such as acid chloride (e.g., l-menthoxyacetyl chloride, etc.) or acid anhydride and the like.

The object compounds (I) of the present invention are novel and exhibit pharmacological activities such as K^+ channel activator action (e.g. vasodilating activity, etc.) and long duration, and therefore are of use for treating or preventing vascular disorders such as hypertension, angina pectoris, cardiac insufficiency, peripheral and cerebral vascular diseases, atherosclerosis, arrhythmia, and the like.

Further, it is expected that the object compound (I) of the present invention are of use for treating or preventing disorders of smooth muscle such as ulcer, asthma, early uterine contraction and incontinence; alopecia; and the like.

In order to illustrate the usefulness of the object compound (I), pharmacological activity of representative compounds of the present invention are shown below.

[1] Test Compound

(1) 4-(2-Cyanoiminothiazolin-3-yl)-6-mesyl-2,2-dimethyl-2H-1-benzopyran
(2) 4-[N-[1-(Cyanoimino)ethyl]amino]-2,2-dimethyl-2H-1-benzopyran-6-carbonitrile

[2] Test Method

Male Wistar strain rats aged 10-11 weeks, weighing about 250 g were used after going unfed overnight. Under ether anesthesia, polyethylene cannula were inserted in the femoral artery for measuring blood pressure and in the femoral vein for injection of the test compound. About 2 hours after the operation, test

compound was given intravenously. Blood pressure was measured at the femoral artery by means of a pressure transducer and recorded as electrically integrated values of mean arterial pressure.

[3] Test Result

Mean ratios of maximum decrease of blood pressure mmHg) are shown in Table.

Test Compounds	Dose	Effect Max
	(mg/kg)	(%)
(1)	1.0	49.2
(2)	1.0	37.0

For therapeutic administration, the object compounds (I) of the present invention are used in the form of conventional pharmaceutical preparation which contains said compound as an active ingredient, in admixture with pharmaceutically acceptable carriers such as an organic or inorganic solid or liquid excipient which is suitable for oral, parenteral and external administration. The pharmaceutical preparations may be in solid form such as tablet, granule, powder, capsule, or liquid form such as solution, suspension, syrup, emulsion, lemonade and the like.

If needed, there may be included in the above preparations auxiliary substances, stabilizing agents, wetting agents and other commonly used additives such as lactose, citric acid, tartaric acid, stearic acid, magnesium stearate, terra alba, sucrose, corn starch, talc, gelatin, agar, pectin, peanut oil, olive oil, cacao butter, ethylene glycol, and the like.

While the dosage of the compound (I) may vary from and also depend upon the age, conditions of the patient, a kind of diseases, a kind of the compound (I) to be applied, etc. In general amounts between 1 mg and about 1,000 mg or even more per day may be administered to a patient. An average single dose of about 1 mg, 2 mg, 5 mg, 10 mg, 25 mg, 50 mg, 100 mg, 200 mg of the object compound (I) of the present invention may be used in treating diseases.

The following Preparations and Examples are given for the purpose of illustrating the present invention.

Preparation 1

To an ice-cooled solution of 4-methoxybenzenesulfonyl chloride (25 g) in tetrahydrofuran (25 ml) was added dimethylamine (50% solution in water, 25 ml). After addition was complete, the mixture was stirred at 50 °C for 30 minutes. The reaction mixture was concentrated to give 4-methoxy-N,N-dimethylbenzenesulfonamide (38 g).

mp : 68 to 69 °C
IR (Nujol) : 1380, 1160 cm^{-1}
NMR ($CDCl_3$, δ) : 2.68 (6H, s), 3.88 (3H, s), 6.9-7.1 (2H, m), 7.6-7.8 (2H, m)
MASS : 215, 171

Preparation 2

A mixture of 4-methoxy-N,N-dimethylbenzenesulfonamide (37 g) and aluminum chloride (69 g) in benzene (170 ml) was stirred under reflux for 30 minutes. The reaction mixture was poured into ice-water and extracted with ethyl acetate. The combined organic layers were washed with water and brine, dried over anhydrous magnesium sulfate, and concentrated. The residue was purified by recrystallization from toluene to give 4-hydroxy-N,N-dimethylbenzenesulfonamide (26 g).

mp : 90 to 92 °C
IR (Nujol) : 3350 cm^{-1}
NMR ($CDCl_3$, δ) : 2.68 (6H, s), 5.0-60 (1H, br m), 6.9-7.0 (2H, m), 7.5-7.7 (2H, m)
MASS : 201, 157

Anal. Calcd. for $C_8H_{11}NO_3S$:	C 47.75, H 5.51, N 6.96
Found :	C 47.83, H 5.62, N 6.75

Preparation 3

A two-phase mixture of 4-hydroxy-N,N-dimethylbenzenesulfonamide (13 g), 3-chloro-3-methyl-1-butyne (33 g), tetra-n-butylammonium hydrogen sulfate (22 g), and sodium hydroxide (21 g) in a mixture of dichloromethane (195 ml) and water (97.5 ml) was vigorously stirred at room temperature for 48 hours. The organic layer was separated, washed with water and brine, dried over anhydrous magnesium sulfate, and concentrated. The residue was added to n-hexane and pulverized to give N,N-dimethyl-4-(1,1-dimethyl-2-propynyloxy)benzenesulfonamide (6.4 g) mp : 87 to 89 °C
IR (Nujol) : 3280, 3250 cm^{-1}
NMR ($CDCl_3$, δ) : 1.71 (6H, s), 2.66 (1H, s), 2.70 (6H, s), 7.3-7.4 (2H, m), 7.6-7.8 (2H, m)
MASS : 267, 252, 201

Anal. Calcd. for $C_{13}H_{17}NO_3S$:	C 58.40, H 6.41, N 5.24
Found :	C 58.15, H 6.41, N 4.86

Preparation 4

A solution of N,N-dimethyl-4-(1,1-dimethyl-2-propynyloxy)benzenesulfonamide (14 g) in 1,2-dichlorobenzene (28 ml) was stirred at 200 °C for 2 hours. After being cooled to room temperature, the reaction mixture was applied directly onto silica gel and eluted with n-hexane and then n-hexaneethyl acetate (5:1, 1:1, gradient) to give N,N,2,2-tetramethyl-2H-1-benzopyran-6-sulfonamide (12.8 g).
mp : 91 to 93 °C
IR (Nujol) : 1630 cm^{-1}
NMR ($CDCl_3$, δ) : 1.47 (6H, s), 2.70 (6H, s), 5.71 (1H, d, J = 10Hz), 6.34 (1H, d, J = 10Hz), 6.85 (1H, d, J = 8Hz), 7.39 (1H, d, J = 2Hz), 7.50 (1H, dd, J = 2Hz, 8Hz)
MASS : 267, 252, 209

Anal. Calcd. for $C_{13}H_{17}NO_3S$:	C 58.40, H 6.41, N 5.24
Found :	C 58.20, H 6.34, N 4.93

Preparation 5

To a vigorously stirred solution of N,N,2,2-tetramethyl-2H-1-benzopyran-6-sulfonamide (12.8 g) in the mixture of dimethyl sulfoxide (24 ml) and water (2 ml) was added N-bromosuccinimide (9.8 g) in one portion. An exothermic reaction was occurred within a few minutes and stirring was continued for an additional 10 minutes. The reaction mixture was poured into water and extracted with ethyl acetate. The combined organic layers were washed with water and brine, dried over anhydrous magnesium sulfate, and concentrated to afford trans-3-bromo-3,4-dihydro-4-hydroxy-N,N,2,2-tetramethyl-2H-1-benzopyran-6-sulfonamide (19.2 g).
mp : 154 to 155 °C
IR (Nujol) : 3480 cm^{-1}
NMR ($CDCl_3$, δ) : 1.44 (3H, s), 1.64 (3H, s), 2.70 (6H, s), 2.84 (1H, d, J = 4Hz), 4.14 (1H, d, J = 10Hz), 4.95

(1H, dd, J = 4Hz, 10Hz), 6.92 (1H, d, J = 8Hz), 7.62 (1H, dd, J = 2Hz, 8Hz), 7.9-8.0 (1H, m)
MASS : 365, 363, 321, 319

Anal. Calcd. for $C_{13}H_{18}BrNO_4S$:	C 42.87, H 4.98, N 3.85
Found :	C 42.76, H 4.85, N 3.55

Preparation 6

A mixture of trans-3-bromo-3,4-dihydro-4-hydroxy-N,N,2,2-tetramethyl-2H-1-benzopyran-6-sulfonamide (19.2 g), potassium carbonate (15 g) and dimethylformamide (153 ml) was stirred at room temperature for 24 hours and followed by at 35° C for 48 hours. The reaction mixture was poured into water and extracted with ethyl acetate. The combined organic layers were washed with water and brine, dried over anhydrous magnesium sulfate, and concentrated to give 3,4-dihydro-3,4-epoxy-N,N,2,2-tetramethyl-2H-1-benzopyran-6-sulfonamide (4.7 g).
mp : 136 to 137° C
IR (Nujol) : 1610, 1570, 1380, 1150 cm^{-1}
NMR ($CDCl_3$, δ) : 1.31 (3H, s), 1.61 (3H, s), 2.71 (6H, s) 3.56 (1H, d, J = 4Hz), 3.97 (1H, d, J = 4Hz), 6.93 (1H, d, J = 8Hz), 7.66 (1H, dd, J = 2Hz, 8Hz), 7.80 (1H, d, J = 2Hz)
MASS : 283

Anal. Calcd. for $C_{13}H_{17}NO_4S$:	C 55.11, H 6.05, N 4.94
Found :	C 55.03, H 5.97, N 5.01

Preparation 7

A mixture of 3,4-dihydro-3,4-epoxy-6-mesyl-2,2-dimethyl-2H-1-benzopyran (4.0 g), ammonium hydroxide (containing ca. 28% ammonia, 40 ml), and ethanol (20 ml) was stirred at room temperature for 72 hours. The reaction mixture was concentrated, added to diisopropyl ether, and pulverized to give trans-4-amino-3,4-dihydro-3-hydroxy-6-mesyl-2,2-dimethyl-2H-1-benzopyran (4.0 g).
IR (Nujol) : 3340, 3290, 3200 cm^{-1}
NMR (DMSO-d_6, δ) : 1.10 (3H, s), 1.36 (3H, s), 3.02 (3H, s), 2.2-3.8 (3H, br m), 3.12 (1H, d, J = 9Hz), 3.51 (1H, d, J = 9Hz), 6.80 (1H, d, J = 10Hz), 7.53 (1H, dd, J = 3, 10Hz), 8.08 (1H, d, J = 3Hz)

Preparation 8

2,2-Dimethyl-2H-1-benzopyran-6-carbonitrile (10 g) was dissolved in toluene (54 ml), and the solution was cooled to -78° C under a nitrogen atmosphere, to this solution was added diisobutylaluminum hydride (1M solution in toluene, 81 ml) over 30 minutes, and the mixture was stirred at -78° C for 10 minutes. The reaction mixture was quenched at -78° C with ethyl acetate (54 ml) followed by 1M tartaric acid solution in water (100 ml). The cooling bath was removed and the mixture was vigorously stirred for 1 hour. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, and concentrated to give 2,2-dimethyl-2H-1-benzopyran-6-carbaldehyde (9.9 g) as a pale yellow oil, which was used without further purification.
IR (Film) : 1690, 1640 cm^{-1}
NMR ($CDCl_3$, δ) : 1.47 (6H, s), 5.70 (1H, d, J = 10Hz), 6.38 (1H, d, J = 10Hz), 6.86 (1H, d, J = 8Hz), 7.52 (1H, d, J = 2Hz), 7.64 (1H, dd, J = 2, 8Hz), 9.82 (1H, s)
MASS : 188, 173

Preparation 9

To a vigorously stirred solution of 2,2-dimethyl-2H-1-benzopyran-6-carbaldehyde (8.0 g) in dimethyl sulfoxide (43 ml)-water (1.0 ml) was added N-bromosuccinimide (8.3 g) in one portion. After 10 minutes, additional N-bromosuccinimide (4.2 g) was added and the mixture was stirred for an additional 10 minutes. The reaction mixture was poured into water and extracted with ethyl acetate. The combined organic layers were washed with water and brine, dried over anhydrous magnesium sulfate, and concentrated. The residue was purified by silica gel chromatography (elution with chloroform) to give trans-3-bromo-3,4-dihydro-2,2-dimethyl-4-hydroxy-2H-1-benzopyran-6-carbaldehyde (8.0 g).

mp : 125 to 127 °C

IR (Nujol) 3380, 1680 cm^{-1}

NMR ($CDCl_3$, δ) : 1.45 (3H, s), 1.65 (3H, s), 2.2-3.1 (1H, br m), 4.15 (1H, d, J = 10Hz), 4.98 (1H, d, J = 10Hz), 6.92 (1H, d, J = 8Hz), 7.77 (1H, dd, J = 2, 8Hz), 8.06 (1H, br s), 9.88 (1H, s)

MASS : 286, 284, 253, 251

Anal Calcd. for $C_{12}H_{13}BrO_3$:	C 50.55, H 4.60
Found :	C 50.26, H 4.66

Preparation 10

A mixture of trans-3-bromo-3,4-dihydro-2,2-dimethyl-4-hydroxy-2H-1-benzopyran-6-carbaldehyde (6.9 g), potassium carbonate (6.7 g), and dimethylformamide (24 ml) was stirred at room temperature for 48 hours and followed by at 35 °C for 24 hours. The reaction mixture was poured into water and extracted with ethyl acetate. The combined organic layers were washed with water and brine, dried over anhydrous magnesium sulfate, and concentrated. The residue was purified by recrystallization from diisopropyl ether to give 3,4-dihydro-2,2-dimethyl-3,4-epoxy-2H-1-benzopyran-6-carbaldehyde (2.9 g).

mp : 108 to 110 °C

IR (Nujol) : 1680 cm^{-1}

NMR ($CDCl_3$, δ) : 1.31 (3H, s), 1.61 (3H, s), 3.55 (1H, d, J = 4Hz), 3.99 (1H, d, J = 4Hz), 6.92 (1H, d, J = 8Hz), 7.77 (1H, dd, J = 2, 8Hz), 7.92 (1H, d, J = 2Hz), 9.88 (1H, s)

MASS : 204, 189, 173

Anal. Calcd. for $C_{12}H_{12}O_3$:	C 70.57, H 5.92
Found :	C 70.79, H 5.97

Preparation 11

The following compound was obtained according to a similar manner to that of Preparation 5.

trans-3,6-Dibromo-3,4-dihydro-2,2-dimethyl-4-hydroxy-2H-1-benzopyran

mp : 93 to 94 °C

IR (Nujol) : 3200 cm^{-1}

NMR ($CDCl_3$, δ) : 1.39 (3H, s), 1.59 (3H, s), 2.60 (1H, br s), 4.10 (1H, d, J = 9.5Hz), 4.87 (1H, d, J = 9.5Hz), 6.68 (1H, d, J = 8.7Hz), 7.28 (1H, dd, J = 2.4, 8.7Hz), 7.59 (1H, d, J = 2.4Hz)

MASS : 334, 336, 338, 200, 202

Preparation 12

The following compound was obtained according to a similar manner to that of Preparation 6.

6-Bromo-3,4-dihydro-2,2-dimethyl-3,4-epoxy-2H-1-benzopyran

mp : 63 to 64 °C
NMR ($CDCl_3$, δ) : 1.24 (3H, s), 1.57 (3H, s), 3.48 (1H, d, J = 4.3Hz), 3.84 (1H, d, J = 4.3Hz), 6.69 (1H, d, J = 8.6Hz), 7.32 (1H, dd, J = 2.4, 8.6Hz), 7.45 (1H, d, J = 2.4Hz)
MASS : 254, 256

Preparation 13

2,2-Dimethyl-2H-1-benzopyran-6-carbonitrile (12 g) was dissolved in tetrahydrofuran (65 ml). To this solution was added methylmagnesium bromice (3M in diethyl ether, 108 ml) dropwise at room temperature, and then the reaction mixture was stirred at reflux for 0.5 hour. After being cooled to room temperature, the mixture was poured into saturated aqueous ammonium chloride and extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, and concentrated. Purification of the residue by column chromatography on silica gel (elution with 10:1 n-hexane-ethyl acetate) gave 6-acetyl-2,2-dimethyl-2H-1-benzopyran (11 g).
IR (Film) : 1670, 1640 cm^{-1}
NMR ($CDCl_3$, δ) : 1.46 (6H, s), 2.53 (3H, s), 5.66 (1H, d, J = 10Hz), 6.36 (1H, d, J = 10Hz), 6.79 (1H, d, J = 8Hz), 7.62 (1H, d, J = 2Hz), 7.74 (1H, dd, J = 2, 8Hz)
MASS : 202, 187

Preparation 14

The following compound was obtained according to a similar manner to that of Preparation 9.
trans-6-Acetyl-3-bromo-3,4-dihydro-2,2-dimethyl-4-hydroxy-2H-1-benzopyran
mp : 112 to 113 °C
IR (Nujol) : 3330, 3250, 1680 cm^{-1}
NMR ($CDCl_3$, δ) : 1.43 (3H, s), 1.63 (3H, s), 2.55 (3H, s), 2.8-3.8 (1H, br m), 4.13 (1H, d, J = 9Hz), 4.94 (1H, d, J = 9Hz), 6.84 (1H, d, J = 9Hz), 7.83 (1H, dd, J = 2, 9Hz), 8.14 (1H, m)
MASS : 300, 298, 285, 283, 267, 265

Anal Calcd. for $C_{13}H_{15}BrO_3$:	C 52.19, H 5.05
Found :	C 51.75, H 4.90

Preparation 15

The following compound was obtained according to a similar manner to that of Preparation 10.
6-Acetyl-3,4-dihydro-2,2-dimethyl-3,4-epoxy-2H-1-benzopyran
mp : 71 to 72 °C
IR (Nujol) : 1680 cm^{-1}
NMR ($CDCl_3$, δ) : 1.29 (3H, s), 1.60 (3H, s), 2.57 (3H, s), 3.54 (1H, d, J = 4Hz), 3.97 (1H, d, J = 4Hz), 6.85 (1H, d, J = 8Hz), 7.87 (1H, dd, J = 2,8Hz), 8.01 (1H, d, J = 2Hz)
MASS : 218, 203

Anal. Calcd for $C_{13}H_{14}O_3$:	C 71.54, H 6.47
Found :	C 71.21, H 6.48

Preparation 16

The following compound was obtained according to a similar manner to that of Preparation 3.

3-Methyl-3-(4-methylphenoxy)-1-butyne
IR (Film) : 3250, 2100 cm^{-1}
NMR ($CDCl_3$, δ) : 1.72 (6H, s), 2.68 (1H, s), 3.05 (3H, s) 7.3-7.4 (2H, m), 7.8-7.9 (2H, m)
MASS : 238, 223

Preparation 17

To 1.2-dichlorobenzene (230 ml) at 200 °C was added 3-methyl-3-(4-mesylphenoxy)-1-butyne (130 g) dropwise over a period of 1.5 hours, the reaction mixture was stirred at 200 °C for an additional 2 hours followed by removal of 1.2-dichlorobenzene by distillation under reduced pressure. The residue was dissolved in diisopropyl ether (100 ml) and treated with activated carbon. The mixture was filtered and the filtrate afforded the precipitate, which was collected, washed with diisopropyl ether, and dried to give 2,2-dimethyl-6-mesyl-2H-1-benzopyran (77 g).
mp : 69 to 71 °C
IR (Nujol) : 1640 cm^{-1}
NMR ($CDCl_3$, δ) : 1.47 (6H, s), 3.03 (3H, s), 5.73 (1H, d, J = 10Hz), 6.34 (1H, d, J = 10Hz), 6.87 (1H, d, J = 8Hz), 7.54 (1H, d, J = 2Hz), 7.65 (1H, dd, J = 2, 8Hz)

Anal. Calcd. for $C_{12}H_{14}O_3S$:	C 60.48, H 5.92
Found	C 60.41, H 6.06

Preparation 18

2,2-Dimethyl-2H-1-benzopyran-6-carbonitrile (12 g) was dissolved in tetrahydrofuran (65 ml). To this solution was added methylmagnesium bromide (3M in diether ether, 108 ml) dropwise at room temperature, and then the reaction mixture was stirred at reflux for 0.5 hour. After being cooled to room temperature, the mixture was poured into saturated aqueous ammonium chloride and extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, and concentrated. Purification of the residue by column chromatography on silica gel (elution with 10:1 n-hexane-ethyl acetate) gave 6-acetyl-2,2-dimethyl-2H-1-benzopyran (11 g).
IR (Film) : 1670, 1640 cm^{-1}
NMR ($CDCl_3$, δ) : 1.46 (6H, s), 2.53 (3H, s), 5.66 (1H, d, J = 10Hz), 6.36 (1H, d, J = 10Hz), 6.79 (1H, d, J = 8Hz), 7.62 (1H, d, J = 2Hz), 7.74 (1H, dd, J = 2, 8Hz)
MASS : 202, 187

Preparation 19

The following compounds were obtained according to a similar manner to that of Preparation 5.
(1) trans-3-Bromo-3,4-dihydro-4-hydroxy-2,2-dimethyl-6-mesyl-2H-1-benzopyran
mp : 141-143 °C
IR (Nujol) : 3450 cm^{-1}
NMR ($CDCl_3$, δ) : 1.38 (3H, s), 1.58 (3H, s), 3.00 (3H, s), 3.24 (1H, d, J = 5Hz), 4.06 (2H, d, J = 9Hz), 4.89 (1H, dd, J = 5, 9Hz), 6.85 (1H, d, J = 9Hz), 7.67 (1H, dd, J = 3, 9Hz), 8.05 (1H, d, J = 3Hz)
(2) trans-6-Acetyl-3-bromo-3,4-dihydro-4-hydroxy-2,2-dimethyl-2H-1-benzopyran
mp : 112 to 113 °C
IR (Nujol) : 3330, 3250, 1680 cm^{-1}
NMR ($CDCl_3$, δ) : 1.43 (3H, s), 1.63 (3H, s), 2.55 (3H, s), 2.8-3.8 (1H, br m), 4.13 (1H, d, J = 9Hz), 4.94 (1H, d, J = 9Hz), 6.84 (1H, d, J = 9Hz), 7.83 (1H, dd, J = 2, 9Hz), 8.14 (1H, m)
MASS : 300, 298, 285, 283, 267, 265

Anal. Calcd. for $C_{13}H_{15}BrO_3$:	C 52.19, H 5.05
Found :	C 51.75, H 4.90

Preparation 20

The following compounds were obtained according to a similar manner to that of Preparation 6.

(1) 3,4-Dihydro-2,2-dimethyl-3,4-epoxy-6-mesyl-2H-1-benzopyran

mp : 153-155 °C

NMR ($CDCl_3$, δ) : 1.23 (3H, s), 1.53 (3H, s), 2.95 (3H, s), 3.46 (1H, d, J = 5Hz), 3.86 (1H, d, J = 5Hz), 6.83 (1H, d, J = 9Hz), 7.68 (1H, dd, J = 3, 9Hz), 7.83 (1H, d, J = 3Hz)

(2) 6-Acetyl-3,4-dihydro-2,2-dimethyl-3,4-epoxy-2H-1-benzopyran

mp : 71 to 72 °C

IR (Nujol) : 1680 cm^{-1}

NMR ($CDCl_3$, δ) : 1.29 (3H, s), 1.60 (3H, s), 2.57 (3H, s), 3.54 (1H, d, J = 4Hz), 3.97 (1H, d, J = 4Hz), 6.85 (1H, d, J = 8Hz), 7.87 (1H, dd, J = 2, 8Hz), 8.01 (1H, d, J = 2Hz)

MASS : 218, 203

Anal. Calcd. for $C_{13}H_{14}O_3$:	C 71.54, H 6.47
Found :	C 71.21, H 6.48

Preparation 21

The following compounds were obtained according to a similar manner to that of Preparation 7.

(1) trans-4-Amino-3,4-dihydro-3-hydroxy-N,N,2,2-tetramethyl-2H-1-benzopyran-6-sulfonamide

mp : 183 to 184 °C

IR (Nujol) : 3360, 3280 cm^{-1}

NMR (DMSO-d_6, δ) : 1.13 (3H, s), 1.40 (3H, s), 2.00 (2H, s), 2.57 (6H, s), 3.22 (1H, dd, J = 5, 9Hz), 3.56 (1H, d, J = 9Hz), 5.56 (1H, d, J = 5Hz), 6.90 (1H, d, J = 8Hz), 7.45 (1H, dd, J = 2, 8Hz), 7.97 (1H, d, J = 2Hz)

MASS : 300, 282, 267

Anal. Calcd. for $C_{13}H_{20}N_2O_4S$:	
Found :	C 51.98, H 6.71, N 9.33 C 51.77, H 6.57, N 9.09

(2) trans-4-Amino-3,4-dihydro-3-hydroxy-2,2-dimethyl-6-nitro-2H-1-benzopyran

mp : 150 to 151 °C

IR (Nujol) : 3350, 3280, 3070, 1500 cm^{-1}

NMR (DMSO-d_6, δ) : 1.15 (3H, s), 1.42 (3H, s), 1.99 (2H, br s), 3.24 (1H, dd, J = 5, 9Hz), 3.59 (1H, d, J = 9Hz), 5.63 (1H, d, J = 5Hz), 6.90 (1H, d, J = 9Hz), 8.00 (1H, dd, J = 3, 9Hz), 8.50 (1H, dd, J = 1, 3Hz)

MASS : 222 (M+ - 16), 208

Anal. Calcd. for $C_{11}H_{14}N_2O_4$:	
Found :	C 55.46, H 5.92, N 11.76 C 55.13, H 5.93, N 11.66

(3) trans-6-Acetyl-4-amino-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran
mp : 134 to 135 °C
IR (Nujol) : 3350, 3290, 3100, 1650 cm^{-1}
NMR ($CDCl_3$, δ) : 1.24 (3H, s), 1.54 (3H, s), 1.6-2.5 (3H, br m), 2.56 (3H, s), 3.36 (1H, d, J = 10Hz), 3.68 (1H, br d, J = 10Hz), 6 82 (1H, d, J = 8Hz), 7.77 (1H, dd, J = 2, 8Hz), 8.06 (1H, dd, J = 1, 2Hz)
MASS : 235, 220

Anal. Calcd. for $C_{13}H_{17}NO_3$:	
Found :	C 66.36, H 7.28, N 5.95 C 65.86, H 7.15, N 5 92

(4) trans-4-Amino-6-bromo-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran
mp : 130 to 131 °C
IR (Nujol) : 3370, 3280, 3100 cm^{-1}
NMR (DMSO-d_6, δ) : 1.08 (3H, s), 1 36 (3H, s), 3.26 (1H, d, J = 9.4Hz), 3.65 (1H, d, J = 9.4Hz), 4.26 (2H, br s), 5.58 (1H, br s), 6.69 (1H, d, J = 8Hz), 7.27 [1H, dd, J = 2.5, 8.7Hz), 7 71 (1H, br s)
MASS : 271, 273

(5) trans-3,4-Dihydro-2,2-dimethyl-3-hydroxy-4-methylamino-2H-1-benzopyran-6-carbonitrile
mp : 117 to 119 °C
NMR (DMSO-d_6, δ) : 1.13 (3H, s), 1.42 (3H, s), 2.14 (3H, s), 2.44 (1H, br s), 3.62 (2H, m), 5.43 (1H, br s), 6.88 (1H, d, J = 8.5Hz), 7.55 (1H, dd, J = 8.5, 2.1Hz), 7.85 (1H, d, J = 2.1Hz)

(6) trans-4-Amino-3,4-dihydro-3-hydroxy-2,2,6-trimethyl-2H-1-benzopyran NMR (DMSO-d_6, δ) . 1.05 (3H, s), 1.34 (3H, s), 2.21 (3H, s), 2.1 (2H, br s), 3.16 (1H, d, J = 9.3Hz), 3.48 (1H, d, J = 9.3Hz), 5.3 (1H, br), 6.57 (1H, d, J = 8.2Hz), 6.88 (1H, dd, J = 8.2, 1.8Hz), 7.35 (1H, br s)
MASS : 207, 135

(7) Ethyl trans-4-amino-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-6-carboxylate
mp : 233 °C (dec.)
IR (Nujol) : 3360, 3275, 3140, 1710, 1610 cm^{-1}
NMR (DMSO-d_6, δ) : 1.12 (3H, s), 1.31 (3H, t, J = 7.1Hz), 1.40 (3H, s), 2.40 (2H, br s), 3.21 (1H, d, J = 9.4Hz), 3.56 (1H, d, J = 9.4Hz), 4.28 (2H, quartet, J = 7.1Hz), 5.5 (1H, br s), 6.79 (1H, d, J = 8.5Hz), 7.71 (1H, dd, J = 8.5, 2.1Hz), 8.25 (1H, br s)
MASS : 265, 194, 148

Example 1

A mixture of 3,4-dihydro-3,4-epoxy-6-mesyl-2,2-dimethyl-2H-1-benzopyran (1.5 g), 2-(cyanoimino)-thiazolidine (1.1 g), triethylamine (3 ml) and N,N-dimethylformamide (6 ml) was stirred at 100 °C for 5 hours. After cooling, the reaction mixture was poured into water. The precipitate was collected by filtration, washed well with water and dried in vacuo to give trans-4-(2-cyanoiminothiazolidin-3-yl)-3,4-dihydro-3-hydroxy-6-mesyl-2,2-dimethyl-2H-1-benzopyran (1.6 g).
mp : 304 to 307 °C
IR (Nujol) : 3350, 2190 cm^{-1}
NMR (DMSO-d_6, δ) : 1.19 (3H, s), 1.45 (3H, s), 3.17 (3H, s), 3.3-4.1 (5H, m), 5.25 (1H, d, J = 9Hz), 5.99 (1H, d, J = 6Hz), 7.10 (1H, d, J = 9Hz), 7.45 (1H, m), 7.77 (1H, m)
MASS : 381, 363, 348

Anal. Calcd. for $C_{16}H_{19}N_3O_4S_2$:	
Found :	C 50.38, H 5.02, N 11.02, S 16.81 C 50.42, H 4.96, N 11.05, S 16.81

Example 2

A mixture of trans-4-(2-cyanoiminothiazolidin-3-yl)-3,4-dihydro-3-hydroxy-6-mesyl-2,2-dimethyl-2H-1-benzopyran (5.5 g) and acetic anhydride (25 ml) in pyridine (50 ml) was allowed to stand at room temperature overnight. The mixture was concentrated to give a residue of trans-3-acetoxy-4-[2-(cyanoimino)thiazolidin-3-yl]-3,4-dihydro-6-mesyl-2,2-dimethyl-2H-1-benzopyran, which was washed with diisopropyl ether and dried in vacuo. To a suspension of this residue in toluene (21 ml) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (10.5 ml), and the mixture was stirred at 100 °C for 1 hour. After cooling, the reaction mixture was poured into water, extracted with ethyl acetate, washed with water, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by silica gel chromatography using ethyl acetate as an eluent to afford 4-(2-cyanoiminothiazolidin-3-yl)-6-mesyl-2,2-dimethyl-2H-1-benzopyran as a white solid. Recrystallization from 50% aqueous acetonitrile gave the pure product (1.44 g).
mp : 247 to 249 °C
IR (Nujol) : 2170, 1640 cm^{-1}
NMR (DMSO-d_6, δ) : 1.47 (6H, s), 3.19) (3H, s), 3.6-3.8 (2H, m), 4.1-4.3 (2H, m), 6.22 (1H, s), 7.06 (1H, d, J = 9Hz), 7.45 (1H, d, J = 2Hz), 7.74 (1H, dd, J = 2Hz, 9Hz)
MASS : 363, 348

Anal. Calcd. for $C_{15}H_{17}N_3O_3S_2$	
Found :	C 52.87, H 4.71, N 11.56, S 17.64 C 52.92, H 5.18, N 11.77, S 17.85

Example 3

To a solution of 3,4-dihydro-3,4-epoxy-6-mesyl-2,2-dimethyl-2H-1-benzopyran (1.5 g) in dimethyl sulfoxide (30 ml) Was added sodium salt of isothiazolidine 1,1-dioxide (1.7 g). The mixture was stirred at room temperature overnight. Water was carefully added to the reaction mixture and the whole was extracted with ethyl acetate. The extract was washed with water, dried over annhydrous magnesium sulfate, and evaporated in vacuo. The residue was purified by column chromatography on silica gel (50 g) with a mixture of chloroform and methanol (50:1) as eluents to give trans-3,4-dihydro-3-hydroxy-4-(1,1-dioxoisothiazolidin-2-yl)-6-mesyl-2,2-dimethyl-2H-1-benzopyran (0.47 g).
mp : 220 to 221 °C
IR (Nujol) : 3420 cm^{-1}
NMR (DMSO-d_6, δ) : 1.17 (3H, s), 1.45 (3H, s), 2.0-2.5 (2H, m), 2.6-3.0 (2H, s), 3.0-3.4 (2H, m), 3.12 (3H, s), 3.68 (1H, d, J = 9Hz), 4.48 (1H, d, J = 9Hz), 5.64 (1H, s), 6.92 (1H, d, J = 9Hz), 7.6-7.8 (1H, m), 7.8-7.9 (1H, m)

Example 4

A solution of trans-3,4-dihydro-3-hydroxy-4-(1,1-dioxoisothiazolidin-2-yl)-6-mesyl-2,2-dimethyl-2H-1-benzopyran (0.32 g) in pyridine (10 ml) was treated with acetic anhydride (5 ml), and the mixture was stood at room temperature overnight. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed successively with 1N hydrochioric acid, a saturated aqueous solution of sodium bicarbonate and brine, and then dried over anhydrous magnesium sulfate. Removal of the solvent under reduced pressure gave the crude product, which was purified by recrystallization from ethyl acetate to give 4-(1,1-dioxoisothiazolidin-2- yl)-6-mesyl-2,2-dimethyl-2H-1-benzopyran (0.14 g)
mp : 226 to 227 °C
IR (Nujol) : 1640 cm^{-1}
NMR ($CDCl_3$, δ) : 1.50 (6H, s), 2.3-2.6 (2H, m), 3.2-3.6 (4H, m), 5.93 (1H, s), 6.88 (1H, d, J = 9Hz), 7.70 (1H, dd, J = 3, 9Hz), 7.83 (1H, d, J = 3Hz)

Example 5

The following compound was obtained according to a similar manner to that of Example 1.
trans-4-(2-Cyanoiminothiazolidin-3-yl)-3,4-dihydro-3-hydroxy-N,N,2,2-tetramethyl-2H-1-benzopyran-6-sulfonamide
mp : >300 °C
IR (Nujol) : 3300, 2180 cm^{-1}
NMR (DMSO-d_6, δ) : 1.20 (3H, s), 1.47 (3H, s), 2.56 (6H, s), 3.3-3.5 [3H, m), 3.8-4.0 (2H, m), 5 2-5.4 (1H, m), 6.0-6.1 (1H, m), 7.08 (1H, d, J = 8Hz), 7.16 (1H, br s), 7.5-7.7 (1H, m) MASS: 410, 367

Anal. Calcd. for $C_{17}H_{22}N_4O_4S_2$:	
Found :	C 49.74, H 5.40, N 13.65, S 15 62 C 49.68, H 5.34, N 13.40, S 15.81

Example 6

The following compound was obtained according to a similar manner to that of Example 2.
4-(2-Cyanoiminothiazolidin-3-yl)-N,N,2,2-tetramethyl-2H-1-benzopyran-6-sulfonamide
mp : 244 to 245 °C
IR (Nujol) 2180, 1660 cm^{-1}
NMR (DMSO-d_6, δ) : 1.47 (6H, s), 2.57 (6H, s), 3.6-3.8 (2H, m), 4.2-4.4 (2H, m), 6.22 (1H, s), 7.06 (1H, d, J = 8Hz), 7.20 (1H, d, J = 2Hz), 7.57 (1H, dd, J = 2Hz, 8Hz)
MASS : 392, 377, 349

Anal. Calcd. for $C_{17}H_{20}N_4O_3S_2$:	
Found :	C 52.02, H 5.14, N 14.27, S 16.34 C 51.97, H 5.01, N 14.11, S 16.30

Example 7

A solution of trans-4-amino-3,4-dihydro-3-hydroxy-6-mesyl-2,2-dimethyl-2H-1-benzopyran (3.7 g), dimethyl N-cyanoiminodithiocarbonate [$(CH_3S)_2C=NCN$] (2.1 g), and pyridine (14 ml) was stirred under reflux for 3 hours. After being cooled to room temperature, the reaction mixture was concentrated, added to ethyl acetate, and pulverized to give trans-4-(3-cyano-2-methyl-1-isothioureido)-3,4-dihydro-3-hydroxy-6-mesyl-2,2-dimethyl-2H-1-benzopyran (2.7 g).
mp : 219 to 220 °C
IR (Nujol) : 3580, 3460, 3380, 3320, 2170 cm^{-1}
NMR (DMSO-d_6, δ) : 1.09 (3H, s), 1.35 (3H, s), 2.54 (3H, s), 3.07 (3H, s), 3.72 (1H, dd, J = 6, 9Hz), 4.05 [1H, t-like, J = ca. 9Hz), 5.84 (1H, d, J = 6Hz), 6.95 (1H, d, J = 9Hz), 7.50 [1H, br s), 7.65 (1H, dd, J = 3, 9Hz), 8.55 (1H, d, J = 6Hz)

Anal. Calcd. for $C_{15}H_{19}N_3O_4S_2$:	
Found :	C 46.50, H 5.46, N 10.84, S 16.55 C 46.14, H 5.41, N 10.86, S 16.48

Example 8

A mixture of trans-4-(3-cyano-2-methyl-1-isothioureido)-3,4-dihydro-3-hydroxy-6-mesyl-2,2-dimethyl-2H-1-benzopyran (1.0 g) and 40% aqueous methylamine (10 ml) was stirred at 40 °C for 8 hours. The resulting precipitate was collected, washed with ethanol, and dried. Recrystallization from ethanol gave trans-4-(2-cyano-3-methyl-1-guanidino)-3,4-dihydro-3-hydroxy-6-mesyl-2,2-dimethyl-2H-1-benzopyran (0.35 g).
mp : 166 to 168 °C
IR (Nujol) : 3330, 2170 cm^{-1}
NMR (DMSO-d_6, δ) : 1.00 (3H, s), 1.23 (3H, s), 2.59 (3H, d, J = 4Hz), 2.95 (3H, s), 3.54 (1H, dd, J = 6, 10Hz), 4.69 (1H, t, J = 6Hz), 5.56 (1H, d, J = 6Hz), 6.80 (1H, d, J = 9Hz), 6.9-7.3 (2H, m), 7.04 (1H, d, J = 6Hz), 7.47 (1H, s), 7.58 (1H, d, J = 2Hz)

Example 9

The following compound was obtained according to a similar manner to that of Example 8.
trans-4-(2-Cyano-3,3-dimethyl-1-guanidino)-3,4-dihydro-3-hydroxy-6-mesyl-2,2-dimethyl-2H-1-benzopyran
mp : 265 to 268 °C
IR (Nujol) : 3360, 3200, 2180 cm^{-1}
NMR (DMSO-d_6, δ) : 1.16 (3H, s), 1.40 (3H, s), 3.00 (6H, s), 3.09 (3H, s), 3.66 (1H, dd, J = 6, 9Hz), 5.02 (1H, t-like, J = ca. 9Hz), 5.76 (1H, d, J = 6Hz), 6.95 (1H, d, J = 9Hz), 7.21 (1H, d, J = 9Hz), 7.67 (1H, dd, J = 3, 9Hz), 7.7-7.9 (1H, m)

Anal. Calcd. for $C_{15}H_{22}N_4O_4S$:	
Found :	C 52.44, H 6.05, N 15.29 C 52.52, H 5.88, N 15.32

Example 10

The following compounds were obtained according to a similar manner to that of Example 1.

(1) trans-4-(2-Cyanoiminothiazolidin-3-yl)-3,4-dihydro-2,2-dimethyl-3-hydroxy-2H-1-benzopyran-6-carbaldehyde
mp : 270 to 271 °C
IR (Nujol) : 3290, 2170, 1680 cm^{-1}
NMR (DMSO-d_6, δ) : 1.20 (3H, s), 1.47 (3H, s), 3.4-3.6 (3H, m), 3.8-4.0 (2H, m), 5.29 (1H, d, J = 10Hz), 6.04 (1H, d, J = 7Hz), 7.01 (1H, d, J = 8Hz), 7.53 (1H, br s), 7.7-7.8 (1H, m), 9.88 (1H, s)
MASS : 331, 313, 298

Anal. Calcd. for $C_{15}H_{17}N_3O_3S$:	
Found :	C 58.00, H 5.17, N 12.68, S 9.68 C 57.59, H 5.11, N 12.80, S 9.60

(2) trans-6-Bromo-4-(2-cyanoiminothiazolidin-3-yl)-3,4-dihydro-2,2-dimethyl-3-hydroxy-2H-1-benzopyran
mp : 237 to 239 °C (dec.)
IR (Nujol) : 3260, 2195, 1580, 1080 cm^{-1}
NMR (DMSO-d_6, δ) : 1.15 (3H, s), 1.42 (3H, s), 3.4-3.65 (3H, m), 3.7-3.95 (2H, m), 5.21 (1H, d, J = 10.0Hz), 5.94 (1H, d, J = 5.7Hz), 6.80 (1H, d, J = 8.6Hz), 7.04 (1H, br s), 7.37 (1H, d, J = 8.6Hz)
MASS : 382, 384, 363, 365, 348, 350

Anal. Calcd. for $C_{15}H_{15}BrN_3O_2S$:	
Found :	C 47.13, H 4.22, N 10.96 C 47.23, H 4.36, N 10.96

(3) trans-6-Acetyl-4-(2-cyanoiminothiazolidin-3-yl)-3,4-dihydro-2,2-dimethyl-3-hydroxy-2H-1-benzopyran
mp : 197 to 198 °C
IR (Nujol) : 3390, 2180, 1670 cm^{-1}
NMR (DMSO-d_5, δ) : 1.19 (3H, s), 1.47 (3H, s), 2.51 (3H, s), 3.4-3.7 (3H, m), 3.7-4.0 (2H, m), 5.27 (1H, d, J = 10Hz), 6.00 (1H, d, J = 5Hz), 6.94 (1H, d, J = 9Hz), 7.45 (1H, br s), 7.85 (1H, br d, J = 10Hz)
MASS : 327 (M^+ - 18), 312

Anal. Calcd. for $C_{17}H_{13}N_3O_3S$:	
Found :	C 59.11, H 5.54, N 12.16, S 9.28 C 59.52, H 5.56, N 12.21, S 9.25

(4) trans-4-(2-Cyanoiminothiazolidin-3-yl)-3,4-dihydro-2,2-dimethyl-3-hydroxy-6-nitro-2H-1-benzopyran
mp : 264 to 266 °C
IR (Nujol) : 3250, 3100, 2180 cm^{-1}
NMR (DMSO-d_5, δ) : 1.22 (3H, s), 1.49 (3H, s), 3.55 (4H, br s), 3.90 (1H, br s), 5.30 (1H, br d, J = 10Hz), 6.10 (1H, br d, J = 6Hz), 7.05 (1H, d, J = 8Hz), 7.73 (1H, br s), 8.10 (1H, dd, J = 2, 8Hz)
MASS : 348, 330, 315

Anal. Calcd. for $C_{15}H_{15}N_4O_4S$:	
Found :	C 51.72, H 4.63, N 16.08 C 51.36, H 4.71, N 15.12

(5) Ethyl trans-4-(2-cyanoiminothiazolidin-3-yl)-3,4-dihydro-2,2-dimethyl-3-hydroxy-2H-1-benzopyran-6-carboxylate
mp : 245 to 247 °C
IR (Nujol) : 3390, 2180, 1695, 1610 cm^{-1}
NMR (DMSO-d_6, δ) : 1.18 (3H, s), 1.29 (3H, t, J = 7.0Hz), 1.46 (3H, s), 3.3-3.7 (3H, m), 3.7-4.1 (2H, m), 4.28 (2H, q, J = 7.0Hz), 5.28 (1H, d, J = 10.0Hz), 6.01 (1H, d, J = 5.7Hz), 6.94 (1H, d, J = 8.6Hz), 7.46 (1H, br s), 7.79 (1H, br d, J = 8.6Hz)
MASS : 375, 357, 342, 296

Anal. Calcd. for $C_{18}H_{21}N_3O_4S$:	
Found :	C 57.59, H 5.64, N 11.19 C 57.41, H 5.52, N 11.17

Example 11

The following compounds were obtained according to a similar manner to that of Example 2.

(1) 4-(2-Cyanoiminothiazolidin-3-yl)-2,2-dimethyl-2H-1-benzopyran-6-carbaldehyde
mp : 230 to 231 °C
IR (Nujol) : 2180, 1680, 1650 cm^{-1}

NMR (DMSO-d_6, δ) : 1.48 (6H, s), 3.72 (2H, br t, J = 7Hz), 4.20 (2H, t, J = 7Hz), 6.19 (1H, s), 7.03 (1H, d, J = 8Hz), 7.55 (1H, d, J = 2Hz), 7.78 (1H, dd, J = 2, 8Hz), 9.88 (1H, s)
MASS : 313, 298, 270

Anal. Calcd. for $C_{17}H_{15}N_3O_2S$:	
Found :	C 61.32, H 4.82, N 13.41, S 10.23 C 61.14, H 4.79, N 13.05, S 10.36

(2) 6-Bromo-4-(2-cyanoiminothiazolidin-3-yl)-2,2-dimethyl-2H-1-benzopyran
mp : 205 to 207 °C
IR (Nujol) : 2180, 1660 cm^{-1}
NMR (DMSO-d_6, δ) : 1.42 (6H, s), 3.70 (2H, br t, J = 7.4Hz), 4.17 (2H, t, J = 7.4Hz), 6.12 (1H, s), 6.81 (1H, d, J = 8.6Hz), 7.17 (1H, d, J = 2.4Hz), 7.36 (1H, dd, J = 2.4, 8.6Hz)
MASS : 363, 365, 348, 350

Anal. Calcd. for $C_{15}H_{14}BrN_3OS$:	
Found :	C 49.46, H 3.87, N 11.54 C 49.37, H 3.86, N 11.23

(3) 6-Acetyl-4-(2-cyanoiminothiazolidin-3-yl)-2,2-dimethyl-2H-1-benzopyran
mp : 209 to 211 °C
IR (Nujol) : 2180, 1680 cm^{-1}
NMR (DMSO-d_6, δ) : 1.46 (6H, s), 2.52 (3H, s), 3.72 (2H, t, J = 7Hz), 4.20 (2H, t, J = 7Hz), 6.16 (1H, s), 6.96 (1H, d, J = 8Hz), 7.48 (1H, d, J = 2Hz), 7.86 (1H, dd, J = 2, 8Hz)
MASS : 327, 312

Anal. Calcd. for $C_{17}H_{17}N_3O_2S$:	
Found :	C 62.37, H 5.23, N 12.83 C 62.69, H 5.31, N 12.75

(4) 4-(2-Cyanoiminothiazolidin-3-yl)-2,2-dimethyl-6-nitro-2H-1-benzopyran
mp : 212 to 213 °C
IR (Nujol) : 2190, 1660 cm^{-1}
NMR (DMSO-d_6, δ) : 1.49 (6H, s), 3.74 (2H, br t, J = 7Hz), 4.24 (2H, t, J = 7Hz), 6.30 (1H, s), 7.06 (1H, d, J = 8Hz), 7.79 (1H, d, J = 2Hz), 8.11 (1H, dd, J = 2, 8Hz)
MASS : 330, 315

Anal. Calcd. for $C_{15}H_{14}N_4O_3S$:	
Found :	C 54.54, H 4.27, N 16.96, S 9.71 C 54.49, H 4.39, N 15.98, S 9.86

Example 12

A mixture of trans-4-amino-3,4-dihydro-2,2-dimethyl-3-hydroxy-2H-1-benzopyran-6-carbonitrile (15.28 g) and ethyl N-cyanoacetimidate (9.42 g) in pyridine (70 ml) was refluxed under nitrogen atmosphere for 9 hours. The mixture was cooled to room temperature and concentrated under reduced pressure. The residue

was dissolved in ethyl acetate (150 ml), washed with 5% hydrochloric acid (100 ml), water (100 ml), and brine (100 ml), successively. The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was recrystallized from ethyl acetate to give trans-4-[N-[1-(cyanoimino)ethyl]amino]-3,4-dihydro-2,2-dimethyl-3-hydroxy-2H-1-benzopyran-6-carbonitrile (12.68 g).
mp : 236-238 °C
NMR (DMSO-d_6, δ) : 1.19 (3H, s), 1.42 (3H, s), 2.35 (3H, s), 3.59 (1H, dd, J = 9, 5.5Hz), 4.99 (1H, t, J = 9Hz), 5.85 (1H, d, J = 5.5Hz), 6.94 (1H, d, J = 9Hz), 7.55-7.7 (2H, m), 9.14 (1H, d, J = 9Hz)
MASS : 266, 251, 210

Example 13

A mixture of trans-4-[N-[1-(cyanoimino)ethyl]amino]-3,4-dihydro-2,2-dimethyl-3-hydroxy-2H-1-benzopyran-6-carbonitrile (0.53 g) and acetic anhydride (0.38 g) in dry pyridine (2.65 ml) was stirred at room temperature for 8 hours. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in ethyl acetate, washed with 5% hydrochloric acid, saturated aqueous sodium bicarbonate, and brine, successively. The extract was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was pulverized with diisopropyl ether and collected by filtration to give trans-3-acetoxy-4-[N-[1-(cyanoimino)ethyl]amino]-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran-6-carbonitrile (0.55 g).
mp : 236-237.5 °C
IR (Nujol) : 3225, 3100, 2225, 2160, 1745 cm^{-1}
NMR (DMSO-d_6, δ) : 1.27 (3H, s), 1.35 (3H, s), 2.09 (3H, s), 2.28 (3H, s), 5.05-5.25 (2H, m), 7.02 (1H, d, J = 8.5Hz), 7.70 (1H, dd, J = 8.5, 2Hz), 7.77 (1H, br s), 9.22 (1H, s)
Mass : 266, 251, 210

Example 14

A mixture of trans-3-acetoxy-4-[N-[1-(cyanoimino)ethyl]amino]-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran-6-carbonitrile (0.49 g) and 1,8-diazabicyclo[5.4.0]-7- undecene (0.46 g) in toluene (10 ml) was stirred at 80 °C for 4 hours, at 90 °C for 2 hours and at 100 °C for additional 2 hours. The resulting mixture was concentrated under reduced pressure. The residue was dissolved in ethyl acetate and then washed with 5% hydrochloric acid,aqueous saturated sodium bicarbonate solution, and brine, successively. The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue (0.31 g) was subjected to column chromatography on silica gel (31 g) and eluted with a mixture of chloroform and methanol (40:1). The fractions containing the desired compound were collected and concentrated under reduced pressure to give powders (0.21 g), which were recrystallized from ethanol to give 4-[N-[1-(cyanoimino)ethyl]amino]-2,2-dimethyl-2H-1-benzopyran-6-carbonitrile (0.17 g).
mp : 205-206 °C
IR (Nujol) : 3200, 3050, 2230, 2190, 1640, 1580 cm^{-1}
NMR (DMSO-d_6, δ) : 1.45 (6H, s), 2.42 (3H, s), 6.06 (1H, s), 6.97 (1H, d, J = 8.3Hz), 7.65 (1H, dd, J = 8.3Hz, J = 2Hz), 7.69 (1H, d, J = 2Hz), 10.02 (1H, s)
MASS : 266, 251, 224, 210

Anal. Calcd. for $C_{15}H_{14}N_4O$:	
Found :	C 67.65, H 5.30, N 21.04 C 67.89, H 5.30, N 21.05

Example 15

A mixture of trans-4-amino-3,4-dihydro-2,2-dimethyl-3-hydroxy-2H-1-benzopyran-6-carbonitrile (4.37 g) and ethyl N-cyanopropionimidate (2.65 g) in ethanol (22 ml) was refluxed for 10 hours. The mixture was cooled and concentrated under reduced pressure. The residue was pulverized with ethanol and recrystal-

lized from ethanol to give trans-4-[N-[1-(cyanoimino)propyl]amino]-3,4-dihydro-2,2-dimethyl-3-hydroxy-2H-1-benzopyran-6-carbonitrile (2.81 g).
mp : 122 to 124 °C
IR (Nujol) : 3370, 3300, 2230, 2180 cm^{-1}
NMR (DMSO-d_6, δ) : 1.18 (3H, s), 1.27 (3H, t, J = 7.6Hz), 2.60 (2H, quartet, J = 7.6Hz), 3.63 (1H, dd, J = 9.3Hz), 4.95 (1H, br t, J = 8.4Hz), 5.85 (1H, d, J = 5.9Hz), 6.96 (1H, d, J = 8.5Hz), 7.53 (1H, br s), 7.64 (1H, dd, J = 8.5Hz), 9.05 (1H, d, J = 7.5Hz)
MASS : 298, 280, 265, 229, 210

Anal. Calcd. for $C_{15}H_{13}N_4O_2$:	
Found :	C 64.42, H 6.08, N 18.78 C 64.48, H 6.14, N 18.71

Example 16

To a solution of trans-4-[N-[1-(cyanoimino)propyl]amino]-3,4-dihydro-2,2-dimethyl-3-hydroxy-2H-1-benzopyran-6-carbonitrile (1.49 g) in dry pyridine (7.5 ml) was added dropwise mesyl chloride (0.77 g) under ice-water cooling. The resulting mixture was stirred overnight at room temperature and concentrated under reduced pressure. The residue was dissolved in a mixture of ethyl acetate and washed with 5% hydrochloric acid (twice), aqueous sodium bicarbonate and brine, successively. The organic layer was dried over anhydrous magnesium sulfate and evaporated in vacuo. The residue was recrystallized from ethanol to give trans-4-[N-[1-(cyanoimino)propyl]amino]-3,4-dihydro-2,2-dimethyl-3-mesyloxy-2H-1-benzopyran-6-carbonitrile (1.50 g).
mp : 189 to 190 °C (dec.)
IR (Nujol) : 3300, 2225, 2180 cm^{-1}
NMR (DMSO-d_6, δ) : 1.25 (3H, t, J = 7.7Hz), 1.36 (3H, s), 1.45 (3H, s), 2.58 (2H, quartet, J = 7.7Hz), 3.39 (3H, s), 4.91 (1H, d, J = 5.7Hz), 5.18 (1H, t, J = 6.4Hz), 7.05 (1H, d, J = 8.5Hz), 7.73 (1H, dd, J = 8.5 J = 2.0Hz), 7.82 (1H, d, J = 2.0Hz), 9.26 (1H, d, J = 7.1Hz)
MASS : 280, 265

Anal. Calcd. for $C_{17}H_{20}N_4O_4S$:	
Found :	C 54.24, H 5.36, N 14.88 C 54.38, H 5.30, N 14.77

Example 17

The following compound was obtained according to a similar manner to that of Example 14.
4-[N-[1-(Cyanoimino)propyl]amino]-2,2-dimethyl-2H-1-benzopyran-6-carbonitrile
mp : 171 to 172 °C
IR (Nujol) : 2225, 2180, 1660, cm^{-1}
NMR (DMSO-d_6, δ) : 1.31 (3H, t, J = 7.6Hz), 1.46 (6H, s), 2.70 (2H, quartet, J = 7.6Hz), 6.10 (1H, s), 6.98 (1H, d, J = 8.4Hz), 7.63 (1H, d, J = 20Hz), 7.66 (1H, dd, J = 8.4Hz, J = 2.0Hz), 9.97 (1H, br s)

Anal. Calcd. for $C_{15}H_{15}N_4O$:	
Found :	C 68.55, H 5.75, N 19.99 C 68.48, H 5.87, N 19.92

MASS : 280, 265, 238, 210

Example 18

The following compound was obtained according to a similar manner to that of Example 15.
trans-4-[[(Cyanoimino)(phenyl)methyl]amino]-3,4-dihydro-2,2-dimethyl-3-hydroxy-2H-1-benzopyran-6-carbonitrile
mp : 147 to 150 °C (dec.)
IR (Nujol) : 3470, 3430, 3235, 3075, 2230, 2180, 1610, 1095 cm^{-1}
NMR (DMSO-d_6, δ) : 1.23 (3H, s), 1.45 (3H, s), 3.77 (1H, dd, J = 5.9, 9.3Hz), 5.18 (1H, br t, J = 7.6Hz), 6.05 (1H, d, J = 5.9Hz), 6.97 (1H, d, J = 8.5Hz), 7.55-7.90 (7H, m), 9.43 (1H, d, J = 7.6Hz)
MASS : 346, 328, 313, 276

Example 19

A solution of trans-4-amino-3,4-dihydro-2,2-dimethyl-3-hydroxy-2H-1-benzopyran-6-carbonitrile (5.0 g), methyl N-cyano-4-chlorobutyrimidate (7.36 g), triethylamine (4.8 ml), and toluene (12 ml) was stirred at 100 °C for 2 days. After being cooled to room temperature, the reaction mixture was concentrated. The residue was taken up in ethyl acetate and washed with brine, dried over anhydrous magnesium sulfate, and concentrated. After purification by column chromatography on silica gel (elution with chloroform-methanol 25:1), the crude product was further purified by recrystallization from ethyl acetate to give trans-4-(2-cyanoiminopyrrolidin-1-yl)-3,4-dihydro-2,2-dimethyl-3-hydroxy-2H-1-benzopyran-6-carbonitrile (0.87 g).
mp : 246 to 247 °C
IR (Nujol) : 3350, 2230, 2180, 1600 cm^{-1}
NMR (DMSO-d_6, δ) : 1.19 (3H, s), 1.46 (3H, s), 2.0-2.2 (2H, m), 2.8-3.3 (3H, m), 3.4-3.7 (1H, m), 3.8-4.0 (1H, m), 5.16 (1H, d, J = 10Hz), 5.90 (1H, d, J = 5Hz), 6.97 (1H, d, J = 9Hz), 7.59 (1H, br s), 7.64 (1H, br d, J = 9Hz)
MASS : 292 (M^+ - 18), 277

Anal. Calcd. for $C_{17}H_{13}N_4O_2$:	
Found :	C 65.79, H 5.85, N 18.05 C 65.65, H 5.98, N 17.88

Example 20

The following compounds were obtained according to a similar manner to that of Example 15.
(1) trans-4-[N-[1-(Cyanoimino)butyl]amino]-3,4-dihydro-2,2-dimethyl-3-hydroxy-2H-1-benzopyran-6-carbonitrile
mp : 155 to 158 °C (dec.)
IR (Nujol) : 3385, 3270, 3115, 2225, 2160, 1615, 1075 cm^{-1}
NMR (DMSO-d_6, δ) : 0.99 (3H, t, J = 7.4Hz), 1.19 (3H, s), 1.41 (3H, s), 1.75 (2H, septet, J = 7.4Hz), 2.5-2.75 (2H, m), 3.63 (1H, dd, J = 6.0, 9.2Hz), 4.97 (1H, t, J = 8.4Hz), 5.82 (1H, d, J = 6.02Hz), 6.96 (1H, d, J = 8.5Hz), 7.52 (1H, br s), 7.64 (1H, dd, J = 1.9, 8.5Hz), 9.09 (1H, d, J = 7.9Hz)
MASS : 313, 294, 279

Anal. Calcd. for $C_{17}H_{20}N_4O_2$:	
Found :	C 65.37, H 6.45, N 17.94 C 65.40, H 6.52, N 17.79

(2) trans-4-[N-(Cyanoiminomethyl)amino]-3,4-dihydro-2,2-dimethyl-3-hydroxy-2H-1-benzopyran-6-carbonitrile
mp : 142 to 147 °C (dec.)
IR (Nujol) : 3270, 2200, 1610 cm^{-1}
NMR (DMSO-d_6, δ) : 1.14 and 1.18 (total 3H, each s), 1.41 (3H, s), 3.62 (1H, dd, J = 6.0, 9.4Hz), 4.46 (1.3H, d, J = 9.4Hz), 4.96 (2.3H, d, J = 9.4Hz), 5.88 (2/3H, d, J = 6.0Hz), 6.06 (1.3H, d, J = 6.0Hz), 6.95 (1H, d, J = 8.5Hz), 7.55-7.8 (2H, m), 8.45 (1.3H, br s), 8.60 (2/3H, s), 9.36 (1H, br s)
MASS : 270, 252, 237

(3) trans-4-[N-[1-(Cyanoimino)ethyl]amino]-3,4-dihydro-2,2-dimethyl-3-hydroxy-6-mesyl-2H-1-benzopyran
mp : 246 to 248 °C
IR (Nujol) : 3340, 3300, 3140, 2180 cm^{-1}
NMR [DMSO-d_6, δ) : 1.19 (3H, s), 1.42 (3H, s), 2.34 (3H, s), 3.17 (3H, s), 3.60 (1H, dd, J = 6, 9Hz), 5.02 (1H, t-like, J = ca. 8Hz), 5.86 (1H, d, J = 6Hz), 7.01 (1H, d, J = 9Hz), 7.60 (1H, d, J = 2Hz), 7.73 (1H, dd, J = 2, 9Hz), 9.21 (1H, d, J = 8Hz)
MASS : 319 (M^+ - 18), 304

Anal. Calcd. for $C_{15}H_{13}N_3O_4S$:	
Found :	C 53.40, H 5.68, N 12.45 C 53.01, H 5.68, N 12.17

(4) trans-4-[N-[1-(Cyanoimino)ethyl]amino]-3,4-dihydro-3-hydroxy-N,N-2,2-tetramethyl-2H-1-benzopyran-6-sulfonamide
mp : 220 to 221 °C
IR (Nujol) : 3330, 2200 cm^{-1}
NMR (DMSO-d_6, δ) : 1.20 (3H, s), 1.43 (3H, s), 2.33 (3H, s), 2.57 (6H, s), 3.66 (1H, dd, J = 4, 5Hz), 4.9-5.0 (1H, m), 5.88 (1H, d, J = 5Hz), 7.00 (1H, d, J = 8Hz), 7.38 (1H, d, J = 2Hz), 7.54 (1H, dd, J = 2, 8Hz), 9.23 (1H, d, J = 8Hz)
MASS : 366, 333

Anal. Calcd. for $C_{15}H_{22}N_4O_4S$:	
Found :	C 52.44, H 6.05, N 15.29 C 52.19, H 6.02, N 15.03

(5) trans-4-[N-[1-(Cyanoimino)ethyl]amino]-3,4-dihydro-3-hydroxy-2,2-dimethyl-6-nitro-2H-1-benzopyran
mp : 155 to 157 °C
IR (Nujol) : 3570, 3400, 3230, 3080, 2200, 1520 cm^{-1}
NMR (DMSO-d_6, δ) : 1.22 (3H, s), 1.45 (3H, s), 2.37 (3H, s), 3.67 (1H, dd, J = 5, 8Hz), 5.02 (1H, br t, J = 8Hz), 5.94 (1H, d, J = 5Hz), 7.01 (1H, d, J = 9Hz), 7.97 (1H, d, J = 3Hz), 8.09 (1H, dd, J = 3, 9Hz), 9.26 (1H, br d, J = 8Hz)
MASS : 304, 286, 271

(6) trans-6-Acetyl-4-[N-[1-(cyancimino)ethyl]amino]-3,4- dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran
mp : 199 to 201 °C
IR (Nujol) : 3420, 3300, 3130, 2190, 1660 cm^{-1}
NMR (DMSO-d_6, δ) : 1.18 (3H, s), 1.41 (3H, s), 2.35 (3H, s), 2.50 (3H, s), 3.61 (1H, dd, J = 6, 9Hz), 5.00 (1H, t, J = 9Hz), 5.80 (1H, d, J = 6Hz), 6.89 (1H, d, J = 9Hz), 7.67 (1H, br s), 7.82 (1H, dd, J = 2, 9Hz), 9.18 (1H, d, J = 9Hz)
MASS : 301, 283, 268

Anal. Calcd. for $C_{15}H_{19}N_3O_3$:	
Found :	C 63.77, H 6.35, N 13.94 C 63.64, H 6.39, N 13.68

(7) trans-6-Bromo-4-[N-[1-(cyanoimino)ethyl]amino]-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran

mp . 252 to 254° C (dec.)

IR (Nujol) : 3475, 3220, 3080, 2175, 1085 cm^{-1}

NMR (DMSO-d_6, δ) : 1.13 (3H, s), 1.36 (3H, s), 2.31 (3H, s), 3.54 (1H, dd, J=6, 9Hz), 4.94 (1H, t, J=9Hz), 5.68 (1H, d, J=6Hz), 6.72 (1H, t, J=8Hz), 7.18 (1H, d, J=2Hz), 7.31 (1H, dd, J=2, 8Hz), 9.08 (1H, d, J=9Hz)

MASS : 337, 339, 319, 321, 304, 306

Anal. Calcd. for $C_{14}H_{15}BrN_3O_2$:	
Found :	C 49.72, H 4.77, N 12.42 C 49.32, H 4.81, N 11.86

Example 21

The following compounds were obtained according to a similar manner to that of Example 16.

(1) trans-4-[[(Cyanoimino)(phenyl)methyl]amino]-3,4-dihydro-2,2-dimethyl-3-mesyloxy-2H-1-benzopyran-6-carbonitrile

mp : 216 to 217° C (dec.)

IR (Nujol) 3290, 2220, 2175, 1608, 1340 cm^{-1}

NMR (DMSO-d_6, δ) : 1.39 (3H, s), 1.50 (3H, s), 3.41 (3H, s), 5.07 (1H, d, J=6.1Hz), 5.41 (1H, br t, J=6.5Hz), 7.05 (1H, d, J=8.6Hz), 7.50-7.85 (6H, m), 7.97 (1H, br s), 9.68 (1H, d, J=7.2Hz)

MASS : 217

Anal. Calcd. for $C_{21}H_{22}N_4O_4S$:	
Found :	C 59.42, H 4.75, N 13.20, S 7.55 C 59.49, H 4.75, N 12.91, S 7.80

(2) trans-4-[N-[1-(Cyanoimino)butyl]amino]-3,4-dihydro-2,2-dimethyl-3-mesyloxy-2H-1-benzopyran-6-carbonitrile

mp : 179 to 181° C

IR (Nujol) : 3245, 3100, 2230, 2180 cm^{-1}

NMR (DMSO-d_6, δ) : 0.97 (3H, t, J=7.4Hz), 1.37 (3H, s), 1.43 (3H, s), 1.73 (2H, septet, J=7.4Hz), 2.45-2.65 (2H, m), 3.40 [3H, s), 4.91 (1H, d, J=5.2Hz), 5.16 (1H, t, J=6.0Hz), 7.06 (1H, d, J=8.5Hz), 7.74 (1H, dd, J=2.0, 8.5Hz), 7.78 (1H, br s), 9.30 (1H, d, J=6.8Hz)

MASS : 390, 294, 279

Anal. Calcd. for $C_{18}H_{22}N_4O_4S$:	
Found :	C 55.37, H 5.68, N 14.35 C 55.65, H 5.69, N 14.21

(3) trans-4-(2-Cyanoiminopyrrolidin-1-yl)-3,4-dihydro-2,2-dimethyl-3-mesyloxy-2H-1-benzopyran-6-car-

bonitrile
mp : 243 to 245° C
IR (Nujol) : 2220, 2180, 1580 cm^{-1}
NMR (DMSO-d_6, δ) : 1.28 (3H, s), 1.55 (3H, s), 1.9-2.2 (2H, m), 2.7-3.3 (3H, m), 3.33 (3H, s), 3.4-3.7 (1H, m), 5.0-5.2 (1H, m), 5.5-5.7 (1H, m), 7.06 (1H, d, J = 8Hz), 7.72 (1H, br d, J = 8Hz), 7.77 (1H, br s)
MASS : 309 (M^+ - 79), 292, 277

Example 22

The following compounds were obtained according to a similar manner to that of Example 14.

(1) 4-[[(Cyanoimino)(phenyl)methyl]amino]-2,2-dimethyl-2H-1-benzopyran-6-carbonitrile
mp : 256 to 259° C (dec.)
IR (Nujol) : 3330, 3155, 2220, 2175, 1655, 1610 cm^{-1}
NMR (DMSO-d_6, δ) : 1.49 (6H, s), 6.17 (1H, s), 7.01 (1H, d, J = 8.9Hz), 7.6-8.0 (8H, m)
MASS : 328, 313

Anal. Calcd. for $C_{20}H_{16}N_4O$:	
Found :	C 73.15, H 4.91, N 17.06 C 72.80, H 4.86, N 16.61

(2) 4-[N-[1-(Cyanoimino)butyl]amino]-2,2-dimethyl-2H-1-benzopyran-6-carbonitrile
mp : 131 to 133° C
IR (Nujol) : 3180, 3050, 2225, 2170, 1665, 1600 NMR (DMSO-d_6, δ) : 1.02 (3H, t, J = 7.4Hz), 1.46 (6H, s), 1.79 (2H, septet, J = 7.4Hz), 2.68 (2H, t, J = 7.4Hz), 6.08 (1H, s), 6.99 [1H, d, J = 8.4Hz), 7.60 (1H, d, J = 2.0Hz), 7.67 (1H, dd, J = 2.0, 8.4Hz), 9.97 (1H, br s)
MASS : 294, 279

Anal. Calcd. for $C_{17}H_{18}N_4O$:	
Found :	C 69.37, H 6.16, N 19.03 C 69.36, H 6.29, N 18.96

(3) 4-(2-Cyanoiminopyrrolidin-1-yl)-2,2-dimethyl-2H-1-benzopyran-6-carbonitrile
mp : 267 to 269° C
IR (Nujol) : 2220, 2180, 1660, 1600 cm^{-1}
NMR (DMSO-d_6, δ) : 1.46 (6H, s), 2.1-2.3 (2H, m), 3.03 (2H, t-like, J = ca. 8Hz), 3.81 (2H, t, J = 7Hz), 6.09 (1H, s), 6.99 (1H, d, J = 8Hz), 7.6-7.7 (2H, m)
MASS : 292, 277

Anal. Calcd. for $C_{17}H_{15}N_4O$:	
Found :	C 69.85, H 5.52, N 19.16 C 69.72, H 5.64, N 18.83

Example 23

To a solution of trans-4-[N-(cyanoiminomethyl)amino]-3,4-dihydro-2,2-dimethyl-3-hydroxy-2H-1-benzopyran-6-carbonitrile (1.08 g) in dry pyridine (5.4 ml) was added mesyl chloride (0.77 ml) under ice-water cooling. The reaction mixture was stirred for 2 hours and 20 minutes at ambient temperature and evaporated. The residue was suspended in toluene (26 ml) and thereto was added 1,8-diazabicyclo[5.4.0]-

undec-7-ene (0.89 ml). The reaction mixture was stirred at 70°C for 50 minutes and concentrated under reduced pressure. The residue was dissolved in ethyl acetate and then washed with brine. The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was subjected to a column chromatography on silica gel (28 g) and eluted with a mixture of ethyl acetate and n-hexane (1:4 → 1:1). The fractions containing the object compound were combined and concentrated under reduced pressure. The residue was recrystallized from 50% aqueous ethanol to give 4-[N-(cyanoiminomethyl)amino]-2,2-dimethyl-2H-1-benzopyran-6-carbonitrile (0.38 g).
mp : 159 to 161°C
IR (Nujol) : 2115, 1665, 1635 cm^{-1}
NMR (DMSO-d_6, δ) : 1.45 (3H, s), 1.46 (3H, s), 5.97 (1 2H, s), 6.34 (1 2H, s), 7.00 (1H, d, J = 8.4Hz), 7.6-7.8 (2H, m), 8 53 (1 2H, s), 8.73 (1 2H, br s), 10.60 (1H, br s)
MASS : 252, 237

Example 24

The following compound was obtained according to a similar manner to that of Example 1.
trans-2.2-Dimethyl-4-(1.1-dioxo-1 2.5-thiadiazolidin-2-yl)-3-hydroxy-2H-1-benzopyran-6-carbonitrile
mp : 180 to 183°C
IR (Nujol) · 3560, 3245, 2225, 1162 cm^{-1}
NMR (DMSO-d_6, δ) . 1.18 (3H, s), 1.46 (3H, s), 2.87-3.80 (5H, m), 4.41 (1H, d, J = 10Hz), 5.66 (1H, br s), 6.90 (1H, d, J = 8Hz), 7.14 (1H, br s), 7.59 (1H, dd, J = 2, 8Hz), 7.77 (1H, d, J = 2Hz)
MASS : 323, 290, 252

Anal. Calcd. for $C_{14}H_{17}N_3O_4S$:	
Found :	C 52.00, H 5.30, N 12.99 C 52.09, H 5.29, N 12.86

Example 25

To a solution of 1.1-dioxo-2-methyl-1.2.5-thiadiazolidine (0.89 g) in dimethyl sulfoxide (22 ml) was added 60% sodium hydride (0.26 g) in mineral oil portionwise under water-cooling. The reaction mixture was stirred at ambient temperature for 30 minutes and thereto was added 3.4-dihydro-2.2-dimethyl-3.4-epoxy-2H-1-benzopyran-6-carbonitrile (0.88 g). The reaction mixture was stirred at ambient temperature for 2 days, poured into ice-water (65 g), extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate, and evaporated in vacuo. The residue was subjected to column chromatography on silica gel (45 g) and eluted with a mixture of methanol and chloroform (1:50). The fractions containing object compound were combined and concentrated under reduced pressure. The residue was recrystallized from ethanol to give white crystal of trans-2,2-dimethyl-4-(1,1-dioxo-5-methyl-1,2,5- thiadiazolidin-2-yl)-3-hydroxy-2H-1-benzopyran-6-carbonitrile (0.28 g).
mp : 213 to 214°C
IR (Nujol) : 3520, 2220, 1607, 1275 cm^{-1}
NMR (DMSO-d_6, δ) : 1.17 (3H, s), 1.43 (3H, s), 2.67 (3H, s), 2.83-3.50 (4H, m), 3.64 (1H, dd, J = 6, 10Hz), 4.44 (1H, d, J = 10Hz), 5.80 (1H, d, J = 6Hz), 6.92 (1H, d, J = 8Hz), 7.61 (1H, dd, J = 2, 8Hz), 7.70 (1H, d, J = 2Hz)
MASS : 337, 304, 266

Anal. Calcd. for $C_{15}H_{19}N_3O_4S$:	
Found :	C 53.40, H 5.68, N 12.45 C 52.91, H 5.57, N 12.35

Example 26

The following compounds were obtained according to a similar manner to that of Example 2

(1) 4-[N-[1-(Cyanoimino)ethyl]amino]-2,2-dimethyl-6-mesyl-2H-1-benzopyran

mp : 181 to 182 °C

IR(Nujol) : 3240, 3070, 2180, 1670 cm^{-1}

NMR(DMSO-d_6, δ) : 1.46 (6H, s), 2.44 (3H, s), 3.18 (3H, s), 6.12 (1H, s), 7.04 (1H, d, J = 8Hz), 7.66 (1H, d, J = 2Hz), 7.74 (1H, dd, J = 2, 8Hz), 10.12 (1H, br s)

MASS 319, 304

Anal. Calcd. for $C_{15}H_{17}N_3O_3S$:	
Found :	C 56.41, H 5.36, N 13.16 C 56.16, H 5.36, N 12.90

(2) 4-[N-[1-(Cyanoimino)methyl]amino]-2,2-dimethyl-6-nitro-2H-1-benzopyran

mp : 200 to 201 °C

IR (Nujol) : 3200, 3050, 2170, 1660 cm^{-1}

NMR (DMSO-d_6, δ) : 1.54 (6H, s), 2.58 (3H, s), 6.38 (1H, s), 6.91 (1H, d, J = 10Hz), 7.65 (1H, br s), 8.0-8.1 (2H, m)

MASS : 286, 271, 256

Anal. Calcd. for $C_{14}H_{14}N_4O_3$:	
Found :	C 58.74, H 4.93, N 19.57 C 59.01, H 5.00, N 19.53

(3) 2,2-Dimethyl-4-(1,1-dioxo-5-methyl-1,2,5-thiadiazolidin-2-yl)-2H-1-benzopyran-6-carbonitrile

mp : 147 to 148 °C

IR (Nujol) : 2225, 1637, 1328 cm^{-1}

NMR ($CDCl_3$, δ) : 1.50 (6H, s), 2.83 (3H, s), 3.32-3.74 (4H, m), 6.00 (1H, s), 6.83 (1H, d, J = 8Hz), 7.42 (1H, dd, J = 2, 8Hz), 7.61 (1H, d, J = 2Hz)

MASS : 319, 304

Anal. Calcd. for $C_{15}H_{17}N_3O_3S$:	
Found :	C 56.41, H 5.36, N 13.16 C 56.13, H 5.31, N 13.10

Example 27

The following compounds were obtained according to a similar manner to that of Example 23.

(1) 6-Bromo-4-[N-(1-(cyanoimino)ethyl]amino]-2,2-dimethyl-2H-1-benzopyran

mp : 167 to 169 °C (dec.)

IR (Nujol) : 3185, 2180, 1645 cm^{-1}

NMR [DMSO-d_6, δ) : 1.41 (6H, s), 2.42 (3H, s), 6.03 (1H, s), 6.79 [1H, d, J = 9.2Hz), 7.3-7.4 (2H, m), 9.97 (1H, br s)

MASS : 319, 321, 304, 306

(2) 4-[N-[1-(Cyanoimino)ethyl]amino]-N,N,2,2-tetramethyl-2H-1-benzopyran-6-sulfonamide

mp : 213 to 214 °C

IR (Nujol) : 3220, 3050, 2180, 1670 cm^{-1}

NMR (DMSO-d_6, δ) : 1.47 (6H, s), 2.43 (3H, s), 2.59 (6H, s), 6.03 (1H, s), 7.03 (1H, d, J = 9Hz), 7.37 (1H, d,

J = 2Hz), 7.54 (1H, dd, J = 2, 9Hz), 10.23 (1H, br s)
MASS : 348, 333

Anal. Calcd. for $C_{15}H_{20}N_4O_3S$:	
Found :	C 55.16, H 5.79, N 16.08 C 55.12, H 5.65, N 16.01

Example 28

The following compound was obtained according to a similar manner to that of Example 1.
trans-4-(2-Cyanoiminothiazolidin-3-yl)-3,4-dihydro-3-hydroxy-2,2,6-trimethyl-2H-1-benzopyran
mp : 234 to 235 °C
IR (Nujol) : 3290, 2190, 1570 cm^{-1}
NMR (DMSO-d_6, δ) : 1.12 (3H, s), 1.41 (3H, s), 2.22 (3H, s), 3.3-3.6 (3H, m), 3.65-3.9 (2H, m), 5.17 (1H, d, J = 10.0Hz), 5.83 (1H, d, J = 5.7Hz), 6.65-6.75 (2H, m), 7.00 (1H, br d, J = 8.3Hz)
MASS : 317, 299, 284

Anal. Calcd. for $C_{15}H_{19}N_3O_2S$:	
Found :	C 60.55, H 6.03, N 13.24 C 60.55, H 6.14, N 13.06

Example 29

The following compounds were obtained according to a similar manner to that of Example 15.
(1) trans-4-[N-[1-(Cyanoimino)methyl]amino]-3,4-dihydro-3- hydroxy-2,2,6-trimethyl-2H-1-benzopyran
mp : 243 to 245 °C
IR (Nujol) : 3500, 3240, 3100, 2175 cm^{-1}
NMR(DMSO-d_6, δ) : 1.12 (3H, s), 1.36 (3H, s), 2.20 (3H, s), 2.32 (3H, s), 3.52 (1H, dd, J = 9.3, 5.5Hz), 4.94 (1H, t, J = 9.0Hz), 5.62 (1H, d, J = 5.5Hz), 6.65 (1H, d, J = 8.2Hz), 6.87 (1H, br s), 6.96 (1H, d, J = 8.2Hz), 9.10 (1H, d, J = 8.7Hz)
MASS: 273, 255, 240

(2) 4-[N-[1-(Cyanoimino)ethyl]-N-methylamino]-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-6-carbonitrile
mp : 258 to 259 °C
IR (Nujol) : 3325, 3280, 2225, 2190, 1560 cm^{-1}
NMR (DMSO-d_6, δ) : 1.19, 1.21 (total 3H, each s), 1.45, 1.47 (total 3H, each s), 2.52 (1.8H, s), 2.58 (1.2H, s), 2.62 (1.2H, s), 2.80 (1.8H, s), 3.7-3.8 (1H, m), 4.98 (0.4H, d, J = 9.6Hz), 5.7-5.9 (1H, m), 6.14 (0.4H, d, J = 5.9Hz), 6.9-7.1 (1H, m), 7.5-7.7 (2H, m)
MASS : 298, 280, 265, 221, 56

Anal. Calcd. for $C_{15}H_{18}N_4O_2$:	
Found :	C 64.42, H 6.08, N 18.78 C 64.38, H 6.22, N 18.40

(3) Ethyl trans-4-[N-[1-(cyanoimino)ethyl]amino]-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-6-carboxylate
mp : 194 to 196 °C

IR (Nujol) : 3300, 2190, 1685, 1580 cm^{-1}
NMR (DMSO-d_6, δ) : 1.18 (3H, s), 1.29 (3H, t, J = 7.1Hz), 1.41 (3H, s), 2.35 (3H, s), 3.61 (1H, dd, J = 9.1, 5.5Hz), 4.27 (2H, quartet, J = 7.1Hz), 4.99 (1H, t, J = 8.7Hz), 5.81 (1H, d, J = 5.5Hz), 6.88 (1H, d, J = 8.6Hz), 7.68 (1H, br s), 7.77 (1H, dd, J = 8.6, 2.0Hz), 9.19 (1H, d, J = 8.4Hz)

(4) trans-4-[N-[1-(cyanoimino)-2-methylpropyl]amino]-3,4-dihydro-2,2-dimethyl-3-hydroxy-2H-1-benzopyran-6-carbonitrile
mp : 215 to 216.5 °C
IR (Nujol) : 3225, 3090, 2225, 2190, 1610, 1565 cm^{-1}
NMR (DMSO-d_6, δ) : 1.19 (3H, s), 1.31 (3H, d, J = 7.0Hz), 1.32 (3H, d, J = 7.0Hz), 1.42 (3H, s), 3.09 (1H, septet, J = 7.0Hz), 3.74 (1H, dd, J = 9.3, 6.0Hz), 5.01 (1H, br t, J = 8.7Hz), 5.84 (1H, d, J = 6.0Hz), 6.97 (1H, d, J = 8.5Hz), 7.43 (1H, br s), 7.65 (1H, dd, J = 8.5, 1.9Hz), 8.70 (1H, d, J = 8.2Hz)

Anal. Calcd. for $C_{17}H_{20}N_4O_2$	
Found :	C 65.37, H 6.45, N 17.94 C 64.90, H 6.74, N 17.50

Example 30

The following compound was obtained according to a similar manner to that of Example 16.
trans-4-[N-[1-(Cyanoimino)-2-methylpropyl]amino]-3,4-dihydro-2,2-dimethyl-3-mesyloxy-2H-1-benzopyran-6-carbonitrile
mp : 210 to 211 °C
IR (Nujol) : 3240, 3100, 2225, 2180, 1610, 1550 cm^{-1}
NMR (DMSO-d_6, δ) : 1.29 (3H, d, J = 7.0Hz), 1.30 (3H, d, J = 7.0Hz), 1.34 (3H, s), 1.47 (3H, s), 3.05 (1H, septet, J = 7.0Hz), 3.37 (3H, s), 4.98 (1H, d, J = 6.2Hz), 5.22 (1H, br t, J = 6.5Hz), 7.06 (1H, d, J = 8.2Hz), 7.65-7.8 (2H, m), 8.93 (1H, d, J = 7.1Hz)
MASS : 390, 311, 294, 279

Anal. Calcd. for $C_{18}H_{22}N_4O_4S$:	
Found :	C 55.37, H 5.68, N 14.35 C 55.54, H 5.80, N 14.14

Example 31

The following compound was obtained according to a similar manner to that of Example 2.
4-(2-Cyanoiminothiazolidin-3-yl)-2,2,6-trimethyl-2H-1-benzopyran
mp : 107 to 108 °C
IR (Nujol) : 2170, 1650, 1550 cm^{-1}
NMR (DMSO-d_6, δ) : 1.39 (6H, s), 2.23 (3H, s), 3.69 (2H, t, J = 7.4Hz), 4.14 (2H, t, J = 7.4Hz), 5.98 (1H, s), 6.73 (1H, d, J = 8.1Hz), 6.80 (1H, d, J = 1.7Hz), 7.00 (1H, dd, J = 8.1, 1.7Hz)
MASS : 299, 284

Example 32

The following compound was obtained according to a similar manner to that of Example 14.
4-[N-[1-(Cyanoimino)-2-methylpropyl]amino]-2,2-dimethyl-2H-1-benzopyran-6-carbonitrile
mp : 159 to 160 °C
IR (Nujol) : 3180, 3050, 2225, 2175, 1665, 1560, 1530 cm^{-1}

NMR (DMSO-d_5, δ) : 1.36 (6H, d, J = 6.9Hz), 1.47 (6H, s), 3.11 (1H, septet, J = 6.9Hz), 6.00 (1H, s), 6.99 (1H, d, J = 8.4Hz), 7.41 (1H, d, J = 1.9Hz), 7.66 (1H, dd, J = 8.4, 1.9Hz), 9.75 (1H, s)
MASS : 294, 279

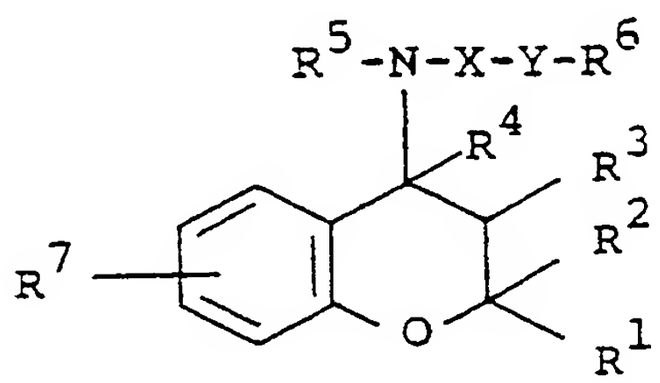
Anal. Calcd. for $C_{17}H_{13}N_4O$:	
Found :	C 69.37, H 6.16, N 19.03 C 69.43, H 6.15, N 19.02

Example 33

A mixture of ethyl 4-(2-cyanoiminothiazolidin-3-yl)-2,2-dimethyl-2H-1-benzopyran-6-carboxylate (1.15 g) and lithium iodide (3.44 g) in 2,6-lutidine (11.5 ml) was refluxed overnight. The resulting mixture was dissolved in a mixture of ethyl acetate and 10% hydrochloric acid, and the organic layer was separated and washed with brine. The extract was dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was purified by column chromatography on silica gel (elution with 30:1 to 4:1 chloroform-methanol) followed by recrystallization from ethanol to give 4-(2-cyanoiminothiazolidin-3-yl)-2,2-dimethyl-2H-1-benzopyran-6-carboxylic acid (0.63 g).
mp : 238 to 239 °C (dec.)
IR (Nujol) : 3320, 2630, 2190, 1710, 1685, 1660, 1610, 1550 cm^{-1}
NMR (DMSO-d_6, δ) : 1.45 (6H, s), 3.70 (2H, t, J = 7.5Hz), 4.20 (2H, t, J = 7.5Hz), 6.14 (1H, s), 6.92 (1H, d, J = 8.4Hz), 7.46 (1H, d, J = 2.0Hz), 7.79 (1H, dd, J = 8.4, 2.0Hz), 12.9 (1H, br s)
MASS : 329, 314, 296

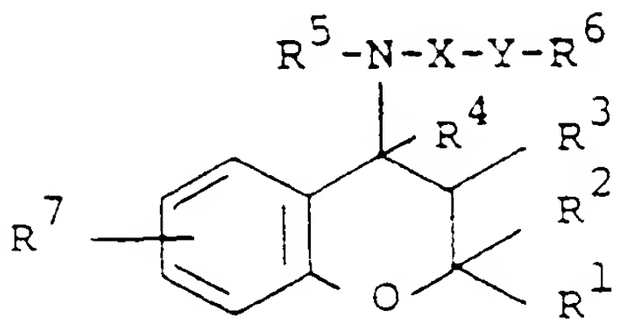
Claims

1 A compound of the formula :



wherein
R^1 and R^2 are each lower alkyl,
R^3 is hydroxy or acyloxy and R^4 is hydrogen, or
R^3 and R^4 are linked together to form a bond,
R^5 is hydrogen or lower alkyl and R^6 is hydrogen, lower alkyl or aryl, or
R^5 and R^6 are linked together to form lower alkylene,
R^7 is cyano, acyl, halogen, nitro or lower alkyl,
X is cyanoiminomethylene or sulfonyl, and
Y is single bond, thio, imino which may have lower alkyl,
provided that
i) when R^7 is cyano, X is cyanoiminomethylene and Y is thio or imino which may have lower alkyl, then R^5 is hydrogen or lower alkyl and R^6 is aryl; and
ii) when R^7 is cyano, R^5 and R^6 are linked together to form lower alkylene and X is sulfonyl, then Y is thio or imino which may have lower alkyl,
and pharmaceutically acceptable salts thereof.

2. A compound of claim 1, which is represented by the formula :



wherein
R^1 and R^2 are each lower alkyl,
R^3 is hydroxy or acyloxy and R^4 is hydrogen, or
R^3 and R^4 are linked together to form a bond,
R^5 is hydrogen or lower alkyl and R^6 is hydrogen, lower alkyl or aryl, or
R^5 and R^6 are linked together to form lower alkylene,
R^7 is acyl, halogen, nitro or lower alkyl,
X is cyanoiminomethylene or sulfonyl, and
Y is single bond, thio, imino which may have lower alkyl,
and pharmaceutically acceptable salts thereof.

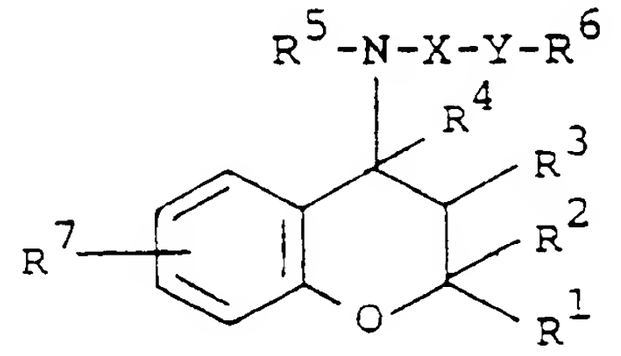
3. A compound of Claim 2, in which
R^3 is hydroxy, lower alkanoyloxy or lower alkylsulfonyloxy and R^4 is hydrogen, or
R^3 and R^4 are linked together to form a bond, and
R^7 is lower alkanoyl, lower alkylsulfonyl, N,N-di(lower)alkylsulfamoyl, lower alkoxycarbonyl, carboxy, halogen, nitro or lower alkyl.

4. A compound of Claim 3, in which
X is cyanoiminomethylene.

5. A compound of Claim 4, in which
R^3 is hydroxy and R^4 is hydrogen, or
R^3 and R^4 are linked together to form a bond,
R^5 and R^6 are linked together to form ethylene, and
Y is thio.

6. A compound of Claim 5, which is selected from the group consisting of :
trans-4-(2-cyanoiminothiazolidin-3-yl)-3,4-dihydro-3-hydroxy-6-mesyl-2,2-dimethyl-2H-1-benzopyran, and
4-(2-cyanoiminothiazolidin-3-yl)-6-mesyl-2,2-dimethyl-2H-1-benzopyran.

7. A compound of claim 1, which is represented by the formula :



wherein
R^1 and R^2 are each lower alkyl,
R^3 is hydroxy or acyloxy and R^4 is hydrogen, or
R^3 and R^4 are linked together to form a bond,
R^5 is hydrogen or lower alkyl and R^6 is hydrogen, lower alkyl or aryl, or
R^5 and R^6 are linked together to form lower alkylene,
R^7 is cyano, and
X is cyanoiminomethylene and Y is single bond, or
X is sulfonyl and Y is imino which may have lower alkyl,
and pharmaceutically acceptable salts thereof.

8. A compound of Claim 7, in which
X is cyanoiminomethylene, and

Y is single bond.

9. A compound of Claim 8, in which

R^3 is hydroxy, lower alkanoyloxy or lower alkylsulfonyloxy and R^4 is hydrogen, or

R^3 and R^4 are linked together to form a bond.

10. A compound of Claim 9, in which

R^5 is hydrogen or lower alkyl, and

R^6 is hydrogen, lower alkyl or aryl.

11. A compound of Claim 10, which is selected from the group consisting of :

trans-4-[N-[1-(cyanoimino)ethyl]amino]-3,4-dihydro-2,2-dimethyl-3-hydroxy-2H-1-benzopyran-6-carbonitrile, and

4-[N-[1-(cyanoimino)ethyl]amino]-2,2-dimethyl-2H-1-benzopyran-6-carbonitrile.

12. A compound of Claim 7, in which

X is sulfonyl, and

Y is imino which may have lower alkyl.

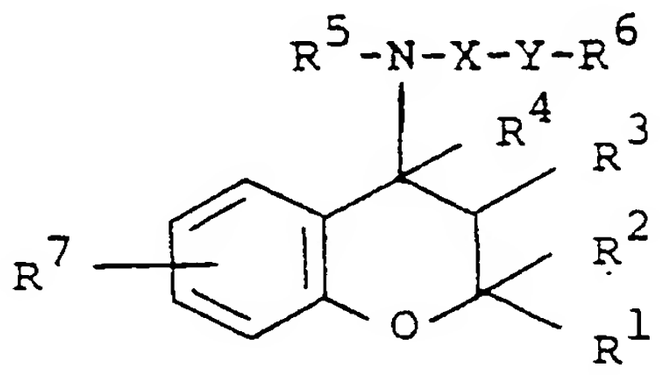
13. A compound of Claim 12, in which

R^3 is hydroxy, lower alkanoyloxy or lower alkylsulfonyloxy and R^4 is hydrogen, or

R^3 and R^4 are linked together to form a bond, and

R^5 and R^6 are linked together to form ethylene.

14. A process for preparing a compound of the formula :



wherein

R^1 and R^2 are each lower alkyl,

R^3 is hydroxy or acyloxy and R^4 is hydrogen, or

R^3 and R^4 are linked together to form a bond,

R^5 is hydrogen or lower alkyl and R^6 is hydrogen, lower alkyl or aryl, or

R^5 and R^6 are linked together to form lower alkylene,

R^7 is cyano, acyl, halogen, nitro or lower alkyl,

X is cyanoiminomethylene or sulfonyl, and

Y is single bond, thio, imino which may have lower alkyl,

provided that

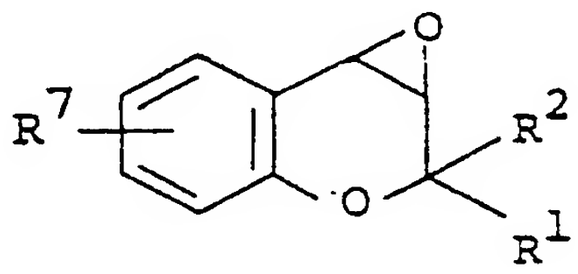
i) when R^7 is cyano, X is cyanoiminomethylene and Y is thio or imino which may have lower alkyl, then R^5 is hydrogen or lower alkyl and R^6 is aryl; and

ii) when R^7 is cyano, R^5 and R^6 are linked together to form lower alkylene and X is sulfonyl, then Y is thio or imino which may have lower alkyl,

or a salt thereof,

which comprises

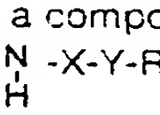
(1) reacting a compound of the formula :



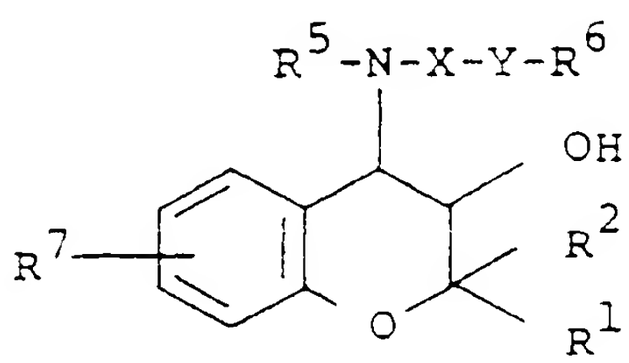
wherein

R^1, R^2 and R^7 are each as defined above,

with a compound of the formula :

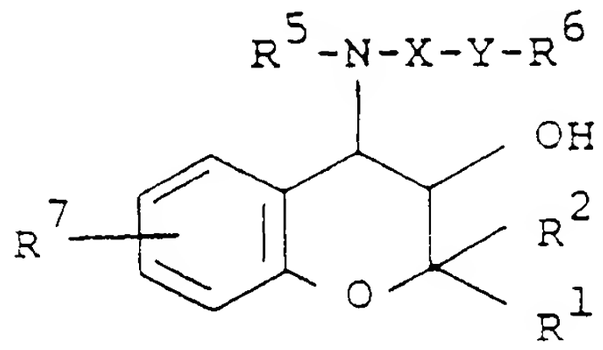


wherein
R^5, R^6, X and Y are each as defined above,
or a salt thereof,
to give a compound of the formula :

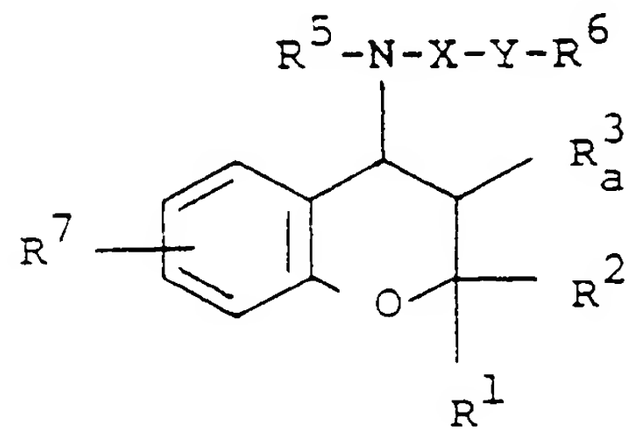


wherein R^1, R^2, R^3, R^5, R^7, X and Y are each as defined above or a salt thereof, or

(2) acylating a compound of the formula :

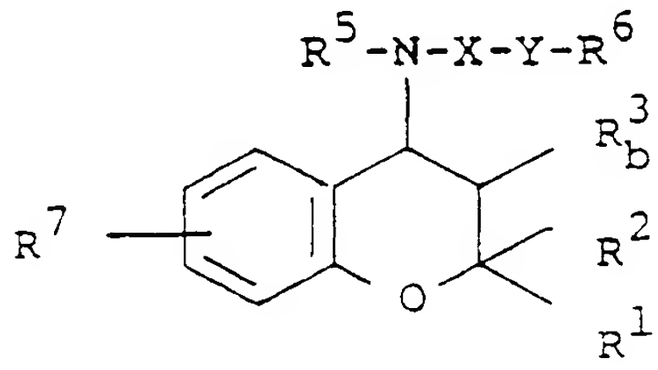


wherein
R^1, R^2, R^5, R^6, R^7, X and Y are each as defined above,
or a salt thereof, to give a compound of the formula:

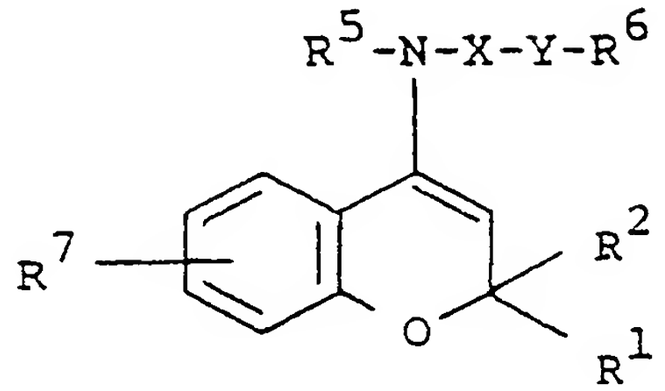


wherein
R^1, R^2, R^5, R^6, R^7, X and Y are each as defined above, and
R^3_a is acyloxy,
or a salt thereof, or

(3) subjecting a compound of the formula :

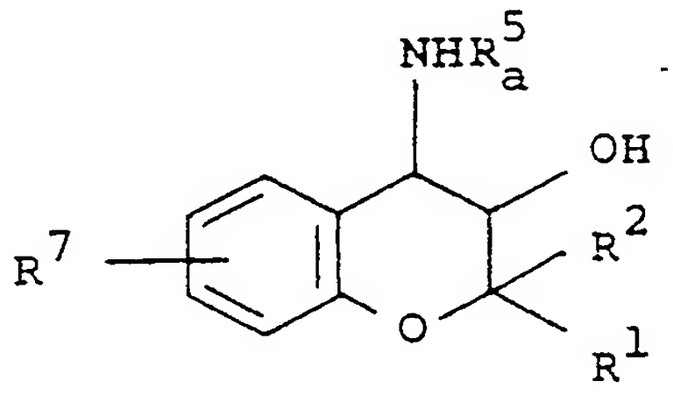


wherein
R^1, R^2, R^5, R^6, R^7, X and Y are each as defined above, and
3^3_5 is hydroxy or acyloxy,
or a salt thereof,
to elimination reaction of a compound of the formula:
3^3_5 - H
wherein
R^3_5 is as defined above,
to give a compound of the formula :

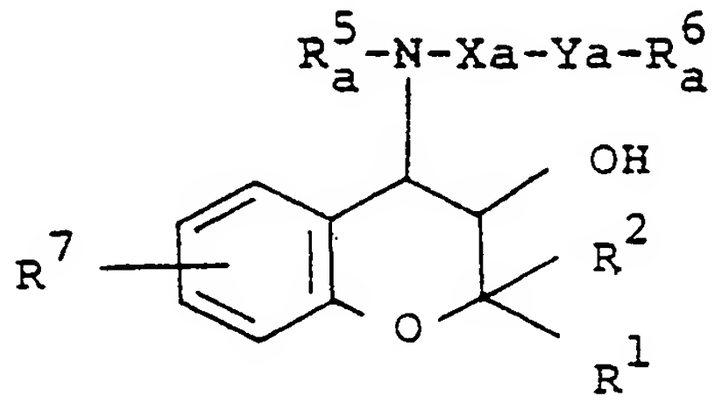


wherein
R^1, R^2, R^5, R^6, R^7, X and Y are each as defined above,
or a salt thereof, or

(4) reacting a compound of the formula :

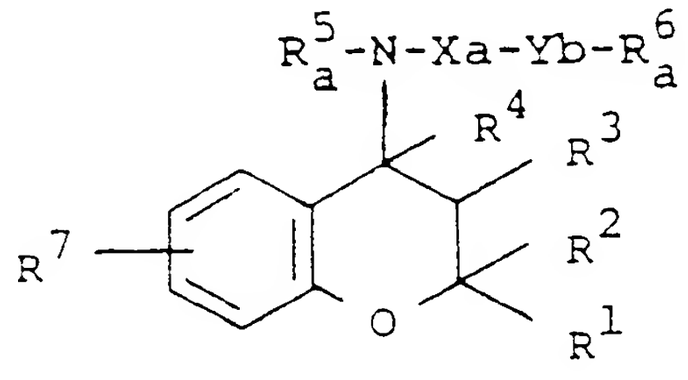


wherein
R^1, R^2 and R^7 are each as defined above, and
R^5_a is hydrogen or lower alkyl,
or a salt thereof,
with a compound of the formula :
Z-Xa-Ya-R^6_a
wherein
R^6_a is hydrogen, lower alkyl or aryl,
Xa is cyanoiminomethylene,
Ya is single bond or thio, and
Z is a leaving group,
to give a compound of the formula :

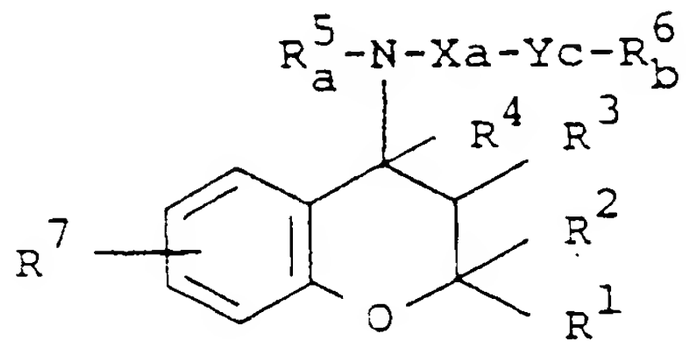


wherein
R^1, R^2, R^5_a, R^6_a, R^7, Xa and Ya are each as defined above,
or a salt thereof, or

(5) reacting a compound of the formula :

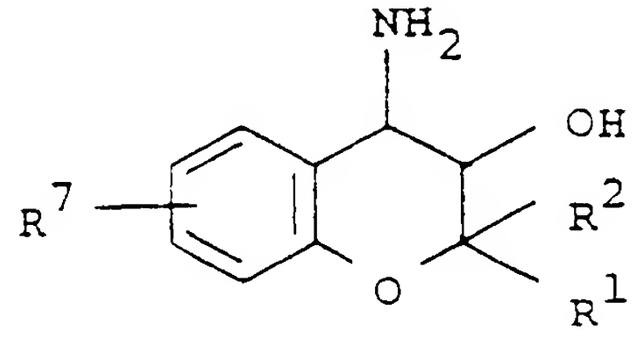


wherein
R^1, R^2, R^3, R^4, R^5_a, R^6_a, R^7 and Xa are each as defined above, and
Yb is thio
or a salt thereof,
with a compound of the formula :
R^6_b -Yc-H
wherein
R^6_b is hydrogen, lower alkyl or aryl, and
Yc is imino which may have lower alkyl
or a salt thereof,
to give a compound of the formula :



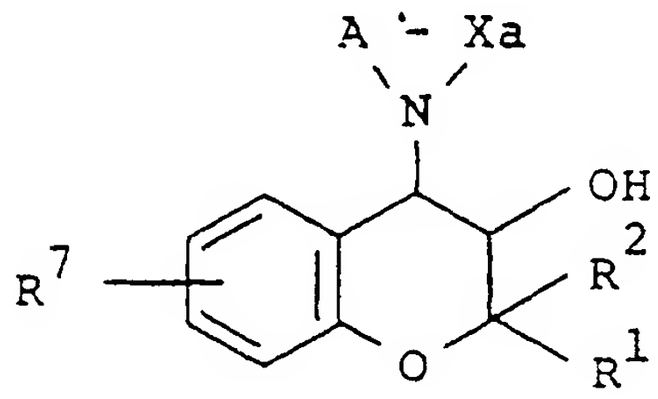
wherein
R^1, R^2, R^3, R^4, R^5_a, R^6_b, R^7, Xa and Yc are each as defined above,
or a salt thereof, or

(6) reacting a compound of the formula :



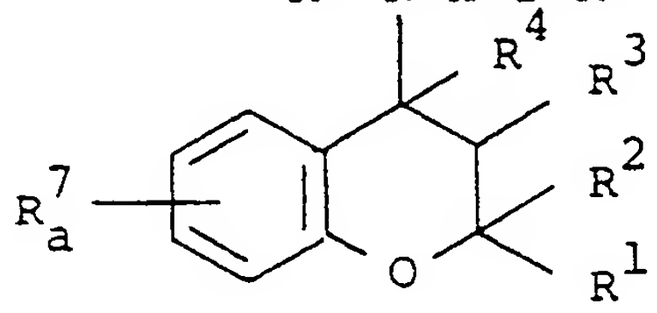
wherein
R^1, R^2 and R^7 are each as defined above,
or a salt thereof,
with a compound of the formula :
$Z\text{-}Xa\text{-}A\text{-}R^8$ wherein
Xa and Z are each as defined above,
R^8 is acid residue, and
A is lower alkylene,

to give a compound of the formula :

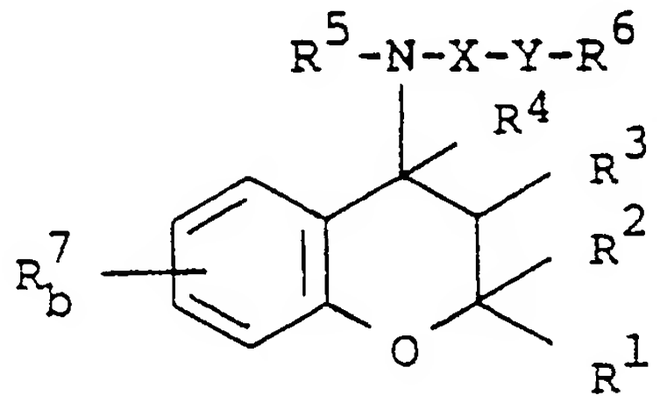


wherein
R^1, R^2, R^7, Xa and A are each as defined above,
or a salt thereof, or

(7) subjecting a compound of the formula :



wherein
R^1, R^2, R^3, R^4, R^5, R^6, X and Y are each as defined above, and
R_a^7 is lower alkoxycarbonyl,
or a salt thereof, to removal reaction of lower alkyl, to give a compound of the formula :



wherein
R^1, R^2, R^3, R^4, R^5, R^6, X and Y are each as defined above, and
R_b^7 is carboxy,
or a salt thereof.

15. A pharmaceutical composition which comprises, as an active ingredient, a compound of claim 1 or a pharmaceutically acceptable salt thereof in admixture with pharmaceutically acceptable carriers.

16. Use a compound of claim 1 or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for therapeutic treatment of K^+ channel mediated diseases.

17. Use of a compound of claim 1 or a pahrmaceutically acceptable salt thereof for the manufacture of a medicament for therapeutic treatment of hypertension.

18. Use of a compound of claim 1 or a pharmaceutically acceptable salt thereof as a medicament.

19. Use of a compound of claim 1 or a pharmaceutically acceptable salt thereof as a K^+ channel activator.

20. Use of a compound of claim 1 or a pharmaceutically acceptable salt thereof as a vasodilating agent.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 90 10 4702

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
A	EP-A-277611 (HOECHST AKTIENGEEESELLSCHAFT) * pages 14 - 17; claims 1, 13 * ---	1, 15	C07D311/68 C07D405/04 C07D417/04 A61K31/35 //(C07D405/04, 311:00,207:00) (C07D417/04, 311:00,277:00
A	EP-A-250077 (BEECHAM GROUP PLC) * pages 1 - 4, line 28 * ---	1, 15	
E	EP-A-359537 (BEECHAM GROUP PLC) * page 1, lines 10 - 63 * -----	1, 15	

TECHNICAL FIELDS SEARCHED (Int. Cl.5)

C07D311/00
C07D405/00
C07D417/00

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
BERLIN	06 JULY 1990	KYRIAKAKOU, G.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

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